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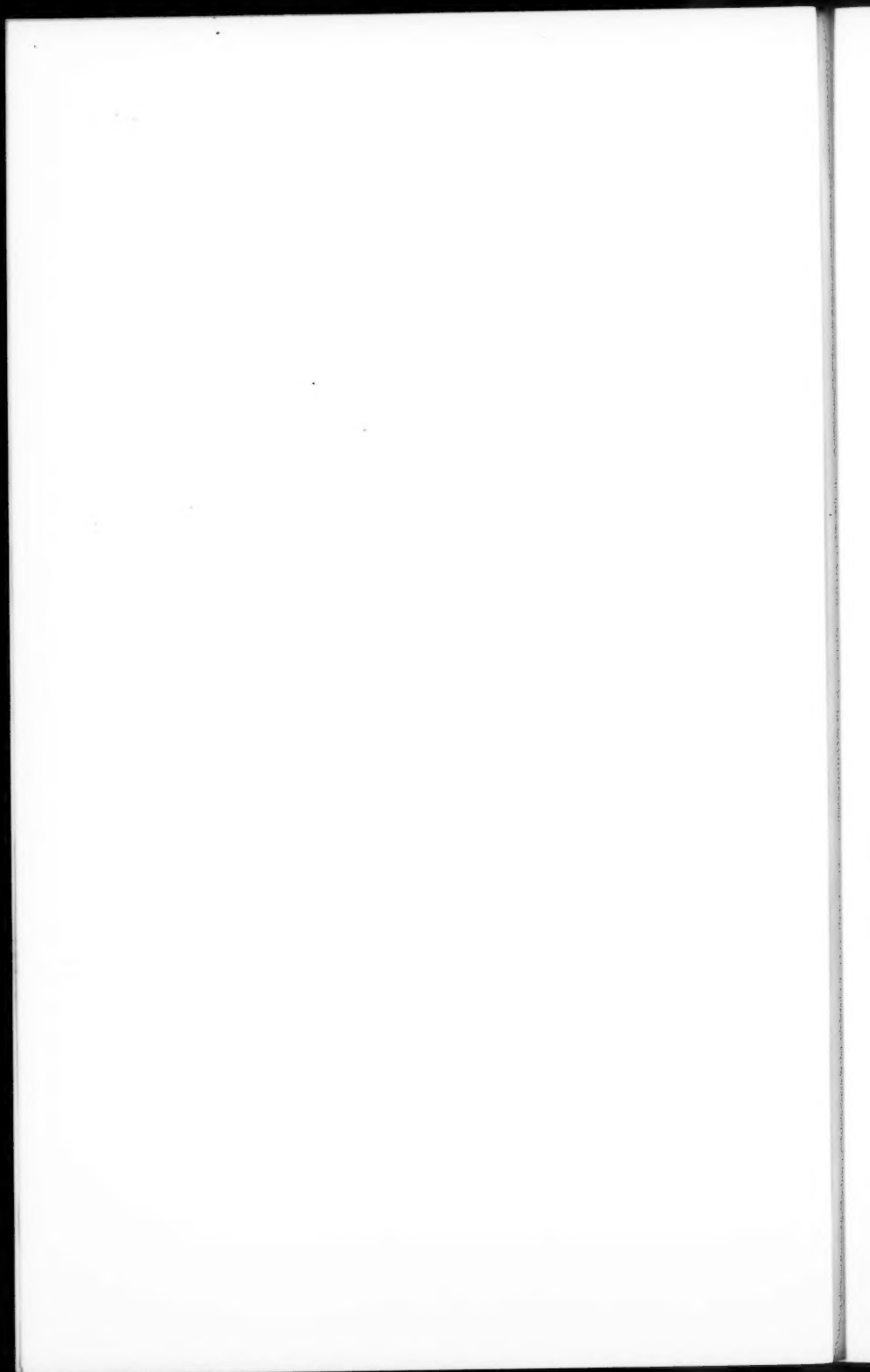
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Elterich, Dr. Theodore O., Pittsburgh, Pa.
Ervin, Dr. Edmund, New York, N. Y.
Esty, Dr. Geoffrey, Westfield, N. J.
Estrin, Dr. Irving Jonathan, New York, N. Y.
Evans, Dr. David P., East Orange, N. J.
Evans, Dr. William, Detroit, Mich.
- Faber, Dr. Harold K., San Francisco, Calif.
Falkenheim, Dr. Curt, Rochester, N. Y.
Farley, Dr. James J., New York, N. Y.
Faverman, Dr. Anita, San Francisco, Calif.
Feilendorf, Dr. Steffy, New York, N. Y.
Feld, Dr. Leo, New York, N. Y.
Felshin, Dr. Gertrude, New York, N. Y.
Ferguson, Dr. Sarah, New York, N. Y.
Fields, Elmore M., Hempstead, N. Y.
Fientz, Dr., New York, N. Y.
Finch, Dr. Clement, Boston, Mass.
Fine, Dr. Hyman P., Perth Amboy, N. J.

Fineman, Dr. Jerome, Baltimore, Md.
Finke, Dr. Walter, Rochester, N. Y.
Finkelstein, Dr. A. H., Baltimore, Md.
Finkelstein, Dr. Marie, Philadelphia, Pa.
Finkelstein, Dr. Malvin, Newark, N. J.
Finkestein, Dr. Marie, Philadelphia, Pa.
Finks, Dr. R. M., San Angelo, Texas.
Finnegan, Dr. John L., Flushing, N. Y.
Fischel, Dr. Edward E., New York, N. Y.
Fischer, Dr. Alfred E., New York, N. Y.
Fisher, Dr. Golda, San Francisco, Calif.
Fisher, Dr. Wilbur J., Buffalo, N. Y.
Fish, Dr. Barbara, New York, N. Y.
Flanagan, Dr. Harold, St. Paul, Minn.
Flechenstine, Dr. R. Jean, Allentown, Pa.
Fleming, Dr. C. L., Penns Grove, N. J.
Florman, Dr. Alfred L., Jackson Heights, N. Y.
Ford, Dr. John R., Gloversville, N. Y.
Forer, Dr. Robert, Trenton, N. J.
Forrest, Dr. Susanne, Kew Gardens, N. Y.
Fost, Dr. William H., Belleville, N. J.
Francis, Jr., Dr. Thomas, Ann Arbor, Mich.
Frank, Dr. Max, Sacramento, Calif.
Frank, Dr. S. Rosa, Beaumont, Texas.
Fredeen, Dr. Robert, Kansas City, Kans.
Frederick, Dr. Doris, American Red Cross, Washington, D. C.
Freud, Dr. Paul, Forest Hills, N. Y.
Freund, Dr. Kate M., New York, N. Y.
Fried, Dr. Joseph H., Brooklyn, N. Y.
Fried, Seymour Dr., New York, N. Y.
Friedman, Dr. Eli, Boston, Mass.
Friedman, Dr. Mary, New York, N. Y.
Friedmann, Dr. Leonard L., Trenton, N. J.
Fries, Dr. Margaret, New York, N. Y.
Frodkin, Dr. Irwin M., Freeport, N. Y.
Frolig, Dr. Hedwig, New York, N. Y.
Funardo, Dr. R., New York, N. Y.
Funaro, Dr. Roberto, New York, N. Y.

Gamble, Dr. James L., Brookline, Mass.
Gardner, Dr. Robt. A., New York, N. Y.
Garthwaite, Dr. Bettina, New York, N. Y.
Garwood, Dr. Norman W., Crossurels, N. J.
Gasul, Dr. Benjamin, Chicago, Ill.

Geilner, Dr. Abraham, Brooklyn, N. Y.
Geisheimer, Dr. Walter, Brooklyn, N. J.
Gelman, Dr. Sidney, Paterson, N. J.
German, Dr. Bernard, Newark, N. J.
Gerner, Dr. Harry E., Jersey City, N. J.
Gerofshin, Dr. Ruth, Brookline, Mass.
Gershberg, Dr. Jacob M., New York, N. Y.
Gersuny, Dr. Otto, New York, N. Y.
Gerstenberger, Dr. Henry J., Cleveland, Ohio.
Geyer, Dr. Robert P., Boston, Mass.
Gibson, Dr. Stanley, Chicago, Ill.
Gilmartin, Dr. J. A., Pittsburgh, Pa.
Ginandes, Dr. George J., New York, N. Y.
Gittleman, Dr. Isaac, Brooklyn, N. Y.
Gingold, Dr. David, Brooklyn, N. Y.
Girodolle, Dr. Roger, New York, N. Y.
Givan, Dr. Thurman, Brooklyn, N. Y.
Glascock, Dr. T., Baltimore, Md.
Glauber, Dr. Richard, Forest Hills, N. Y.
Glickman, Dr. Helene, Springfield, Mass.
Gluck, Dr. Regina, Woodmere, N. Y.
Gluck, Dr. Roland, Brooklyn, N. Y.
Goldfarb, Dr. Arthur A., New York, N. Y.
Goldsborough, Dr. Charles R., Baltimore, Md.
Goldstein, Dr. Harold M., New York, N. Y.
Goldstein, Dr., Baltimore, Md.
Goldstein, Dr. Moe, Forest Hills, N. Y.
Golomb, Dr. Joseph, New York, N. Y.
Goodwin, Dr. T. Campbell, Baltimore, Md.
Goodwin, Dr. D., New York, N. Y.
Goodwin, Dr. Edwin S., Albany N. Y.
Gordon, Dr. Ernest F., Yonkers, N. Y.
Gordon, Dr. Harry H., Denver, Colo.
Gordon, Dr. Samuel, Richmond Hills, N. Y.
Govan, Dr. Clifton Jr., Norfolk, Va.
Graber, Dr. Mary A., Columbus, Ohio.
Greeley, Dr. David M., Orangeburg, N. Y.
Green, Dr. Jacques Henry, Waterbury, Conn.
Greenberg, Lester J. Dr., Far Rockaway, N. Y.
Greenberg, Dr. Morris, New York, N. Y.
Greenberg, Dr. William B., Camp Kilmer, N. J.
Greenberg, Dr. Bernard, Brooklyn, N. Y.
Greenfield, Dr. Nathaniel, New York, N. Y.
Greenspan, Dr. Leon, New York, N. Y.

Greenstein, Dr. Nathan M., New York, N. Y.
Grob, Dr. Otto, Detroit, Mich.
Grozin, Dr. Maurice, Flushing, N. Y.
Grubb, Dr. Samuel P., New York, N. Y.
Gruhn, Dr., New York, N. Y.
Grulee, Dr. Clifford G., Evanston, Ill.
Gross, Dr. Alexander D., New York, N. Y.
Guild, Dr. Harriet G., Baltimore, Md.
Gullickson, Jr., Dr. Glenn, Minneapolis, Minn.
Guntzer, Dr. G. A., New York, N. Y.
Gurley, Dr. Katharine, Jersey City, N. J.
Gustind, Dr. Francis J., Snyder, N. Y.
Gutman, Dr. John, New York, N. Y.
Guy, Dr. Ruth A., New York, N. Y.
Gyorgy, Dr. Paul, Philadelphia, Pa.

Habalyas, Dr. Nicetas Kuo, New York, N. Y.
Haberman, Dr. Sol, Dallas, Texas.
Hall, Dr. Clark H., Oklahoma City, Okla.
Hall, Dr. T., Boston, Mass.
Hall, Dr. Fairfax, New Rochelle, N. Y.
Hamilton, Dr. B. Wallace, New York, N. Y.
Hamilton, Dr. Bengt L. K., Staten Island, N. Y.
Hamre, Dr. Dorothy, New Brunswick, N. J.
Hanks, Dr. J. M., Columbus, Miss.
Hansen, Dr. Arild E., Galveston, Texas.
Hanson, Dr. Alfred, Camden, N. J.
Hanson, Dr. Earl G., Cranford, N. J.
Hardy, Dr. Janet B., Baltimore, Md.
Hardy, Dr. Paul H., New York, N. Y.
Hare, Dr. Kenrick, New York, N. Y.
Harfouche, Dr. Jamal Karam, New York, N. Y.
Harris, Dr. Martin J., Louisville, Ky.
Harris, Dr. S., Philadelphia, Pa.
Harris, Dr. Scott T., Ypsilanti, Mich.
Harris, Dr. T. N., Philadelphia, Pa.
Harrison, Dr. Harold E., Baltimore, Md.
Harriss, Dr. R. R., Hollywood, Fla.
Harper, Dr. Paul, Baltimore, Md.
Hart, Dr., New York, N. Y.
Hart, Dr. Francis B., Brooklyn, N. Y.
Hart, Dr. Lloyd C., Lansing, Mich.
Hartshorn, Dr. W. Morgan, New York, N. Y.
Harvey, Dr. Norman A., Brooklyn, N. Y.

Harvin, Dr. John R., Sumter, S. Carolina.
Harwood, Dr. C., New York, N. Y.
Hauver, Dr. Robert B., Cleveland, Ohio.
Hayden, Dr. Thomas H., Brooklyn, N. Y.
Heafey, Dr. John R., Norwalk, Conn.
Heatley, Dr., New York, N. Y.
Heavenrich, Dr. Robert M., New York, N. Y.
Heffer, Dr. Ernest T., Brooklyn, N. Y.
Heffron, Dr. Roderick, New York, N. Y.
Heiney, Dr. Zelda E., Dayton, Ohio.
Heller, Dr. T. M., New York, N. Y.
Helmholz, Dr. Henry F., Rochester, Minn.
Henley, Dr. Thomas F., Winston-Salem, N. C.
Henze, Dr. C., New York, N. Y.
Herrick, Dr. T. P., Cleveland, Ohio.
Hertig, Dr. Arthur T., Winchester, Mass.
Hertzmark, Dr. Frederic, New York, N. Y.
Hess, Dr. Julius H., Chicago, Ill.
Hetzel, Dr. Joseph L., Waterbury, Conn.
Hewes, Dr. William, Adrian, Mich.
Heymann, Dr. Walter, Cleveland, Ohio.
Higgins, Dr. John M., Sayre, Pa.
Hildick-Smith, Dr. G., New York, N. Y.
Hill, Dr. Miner C., New York, N. Y.
Hill, Dr. Lee Forrest, Des Moines, Iowa.
Hiller, Dr. Eldredge, Washington, D. C.
Himmelstein, Dr. Aaron, New York, N. Y.
Hindman, Dr. Sarah, Bethlehem, Pa.
Hirsch, Dr. Donald, New York, N. Y.
Hirsch, Dr. T. T., New York, N. Y.
Hirshfeld, Dr. L., Glen Gardner, N. J.
Hirschl, Dr. D., New York, N. Y.
Hirschman, Dr. A., New York, N. Y.
Hobby, Dr. Gladys L., Brooklyn, N. Y.
Hodes, Dr. Abra, Staten Island, N. Y.
Hogg, Dr. Paul, Newport News, Va.
Holodnak, Dr. Helen B., New York, N. Y.
Holt Jr., Dr. L. Emmett, New York, N. Y.
Holzsager, Dr. Theodore G., New York, N. Y.
Hoobler, Dr. Icie Macy, Grosse Pointe, Mich.
Howard, Dr. Philip J., Detroit, Mich.
Howitt, Dr. Alice H., Forest Hills, N. Y.
Hubbard, Dr. John P., Washington, D. C.
Hudson, Phoebe, Dr., New York, N. Y.

Huenekens, Dr. E. J., Minneapolis, Minn.
Hull, Dr. Thomas G., Chicago, Ill.
Hummel, Dr. E. G., Camden, N. J.
Hunt, Dr. Andrew D., Philadelphia, Pa.
Hunt, Dr. Fred C., New York, N. Y.
Hunter, Dr. Godel I., New York, N. Y.
Hunter, Dr. Anne F., New York, N. Y.
Hunter, Dr. Thomas H., New York, N. Y.
Hurdak, Dr. Vincent, New York, N. Y.
Hurtado, Jr., Dr. Felix A., Washington, D. C.
Hurwitz, Dr. Samuel, San Francisco, Calif.
Husson, Dr. George, New York, N. Y.
Hyman, Dr. Gordon, H., Chicago, Ill.
Hyman, Dr. Aaron, New York, N. Y.

Iatroy, Dr. C., Trenton, N. J.
Iler, Dr. Russell Hills, Brooklyn, N. Y.
Ingalls, Dr. Theodore H., Boston, Mass.
Ingraham, Dr. Franc D., Boston, Mass.
Israel, Dr. Marvin, Buffalo, N. Y.
Ittner, Dr. Elizabeth, A. J., Brooklyn, N. Y.
Izzo, Dr. Gerard, New York, N. Y.

Jackson, Dr. Herbert F., New York, N. Y.
Jacobs, Dr. Lewis, New Rochelle, N. Y.
Jacobziner, Dr. Harold, New York, N. Y.
Jaeger-Lee, Dr. Dorothy S., Silver Spring, Md.
Janeway, Dr. Charles A., Boston, Mass.
Jeffe, Dr. Joy R., New York, N. Y.
Jenkins, Dr. Leo, New York, N. Y.
Jenkins, Dr. Samuel F., New York, N. Y.
Jensen, Dr. Daniel C., New York, N. Y.
Jeyner, Dr. Edmund, New York, N. Y.
Johnson, Dr. Herbert, New York, N. Y.
Johnson, Dr. Roswell, New Orleans, La.
Jones, Dr. Edmund P., El Paso, Texas.
Jones, Dr. Margaret H., Los Angeles, Calif.
Jordan, Dr. William H., Providence, R. I.
Jorgensen, Dr. Gilbert, M. Los Angeles, Calif.
Joseph, Dr. Marion G., San Francisco, Calif.
Joy, Dr. Genevieve L., College Place, Wash.
Jurist, Dr. Charles, Springfield, Mass.
Julia, Dr. Juan F., New York, N. Y.

Kabnich, Dr. Arthur B., New York, N. Y.
Kagan, Dr. B. M., Chicago, Ill.
Kajdi, Dr. Laslo, Baltimore, Md.
Kantrow, Dr. Abraham H., Flushing, N. Y.
Kaplan, Dr. Arthur A., Utica, N. Y.
Kaplan, Dr. Deborah B., Cortland, N. Y.
Kaplan, Dr. Eugene, New York, N. Y.
Karelitz, Dr. Samuel, New York, N. Y.
Karnofsky, Dr. David A., New York, N. Y.
Karsh, Dr., N. Y. Hospital,
Kastner, Dr. A. L., Milwaukee, Wisc.
Katsampes, Dr. Chris P., Rochester, N. Y.
Katzenstein, Dr. M., New York, N. Y.
Kaufmann, Dr. Else, New York, N. Y.
Kauffman, Dr. Sidney A., Indianapolis, Ind.
Kay, Dr. Maurice N., Providence, R. I.
Kaye, Dr. Robert, Boston, Mass.
Keefer, Dr. Chester S., Boston, Mass.
Keenan, Dr. L. J., Fond du Lac, Wisconsin.
Kelsey, Dr. Weston M., Winston-Salem, N. C.
Kendig, Dr. Edwin L. Jr., Richmond, Va.
Kenyon, Dr. Josephine H., New York, N. Y.
Kerdasha, Dr. George, North Bergen, N. J.
Kerlan, Dr. Irvin, Washington, D. C.
Kerr, Dr. J. De Witt, Lebanon, Pa.
Kessler, Dr. W. R., New York, N. Y.
Kiner, Dr. William E., New York, N. Y.
Kirkpatrick, Dr. C. H., Arcadia, Fla.
Kirmse, Dr. Thomas W., New York, N. Y.
Kitts, Dr. Albert W., Salisbury, Md.
Klein, Dr. Joseph M., Wilkes-Barre, Pa.
Klein, Dr. Reuben I., Chicago, Ill.
Klendshoj, Dr. Niels, Buffalo 4, N. Y.
Knobloch, Dr. Hilda, Brooklyn, N. Y.
Knoblock, Dr. Howard T., Bay City, Mich.
Knowlton, Dr. Abbie Ingalls, New York, N. Y.
Knox, Jr., Dr. J. H. Mason, Baltimore, Md.
Kochenderfer, Dr. Thomas T., Norristown, Pa.
Koenig, Dr. Hedwig, New York, N. Y.
Koenigsberger, Dr. E., Oakland, Calif.
Kohn, Dr. D. Jerome L., New York, N. Y.
Koloski, Dr. Raymond, New York, N. Y.
Konetani, Dr. John, New Orleans, La.
Korn, Dr. Wallace, New York, N. Y.

Kornfeld, Dr. Werner, East Orange, N. J.
Koteen, Dr. Phyllis H., Scarsdale, N. Y.
Kotzen, Dr. Herman F., Reading, Pa.
Krafchik, Dr. Louis, New Brunswick, N. J.
Kramer, Dr. Benjamin, Brooklyn, N. Y.
Kramer, Dr. James G., Akron, Ohio.
Krehbiel, Dr. B. I., Topeka, Kans.
Krugman, Dr. Saul, New York, N. Y.
Kueffner, Dr. Wm., New York, N. Y.
Kurzrok, Dr. Milton (Comdr) USN, Burlingame, Calif.
Kuskin, Dr. Lawrence, Brooklyn, N. Y.
Kutch, Dr. Joseph, New York, N. Y.
Kuttner, Dr. Ann G., Irvington, N. Y.

Lachman, Dr. Joseph, Chester, Pa.
La Grippio, Dr. Gerald A., New York, N. Y.
Lambert, Dr. R. A., New York, N. Y.
Lancaster, Dr. Frank H., Houston, Texas.
Lande, Dr. J. N., Sioux City, Iowa.
Landsberg, Dr. Eva, Brooklyn, N. Y.
Landsberger, Dr. Max, Buffalo, N. Y.
Lang, Dr. Dorothy, White Plains, N. Y.
Langmann, Dr. Alfred G., New York, N. Y.
Lapin, Dr. Jos. H., Bronx, N. Y.
Lapin, Dr. Lottie, New York, N. Y.
Larkin, Dr. Vincent de Paul, New York, N. Y.
Lathrop, Dr. Frederic W., Plainfield, N. J.
Latour, Dr. J. P. A., Boston, Mass.
Lauson, Dr. Henry D., New York, N. Y.
Lawrence, Dr. H. Sherwood, New York, N. Y.
Laws, Dr. Carl H., Brooklyn, N. Y.
Lawson, Dr. Robert B., Winston-Salem, N. C.
Laytner, Dr.,
Lay, Dr. Richard E., Buffalo, N. Y.
Leebron, Dr. J. D., Philadelphia, Pa.
Lehmann, Dr. Theo A., New York, N. Y.
Lehndorff, Dr. Heinrich, New Rochelle, N. Y.
Leinbach, Dr. Harvey, Reading, Pa.
Lemauro, Dr. A., Kingston Ave. Hospital.
Lennox, Dr. Margaret, New Haven, Conn.
Lennox, Dr. William G., Boston, Mass.
Lent, Dr. Virginia C., Hempstead, N. Y.
Leonard, Dr. George N., Miami Beach, Fla.
Leonard, Dr. Martha F., Highland Park, N. J.

Leonard, Dr. Lea, Des Moines, Iowa.
Lessen, Dr. Howard, Brooklyn, N. Y.
Lester, Dr. Charles W., New York, N. Y.
Levens, Dr. Boston, Mass.
Levine, Dr. Philip, Plainfield, N. J.
Levine, Dr. Milton I., New York, N. Y.
Levine, Dr. Samuel Z., New York, N. Y.
Levinsohn, Dr. Sandor A., Paterson, N. J.
Levy, Dr. Anna L., Newark, N. J.
Levy, Dr. Gilbert, Memphis, Tenn.
Levy, Dr. M. L., Baton Rouge, La.
Levy, Dr. Samuel, Brooklyn, N. Y.
Levy, Dr. Walter, New York, N. Y.
Lewis, Dr. Roza A., Baltimore, Md.
Lewis, Dr. Annabelle, Westport, Conn.
Lewis, Dr. Jaques M., New York, N. Y.
Liang, Dr. Shie, New York, N. Y.
Lichtenberg, Dr. Henry H., Washington, D. C.
Lichterman, Dr. Jacob J., Brooklyn, N. Y.
Lichty, Dr. John A., Rochester, N. Y.
Lieberman, Dr. Alfred T., Baltimore, Md.
Lieberman, Dr. Hyman, Brooklyn N. Y.
Liel, Dr. Nina R., Far Rockaway, N. Y.
Lincoln, Dr. Edith M., New York, N. Y.
Lipsitt, Dr. Chas. S., New Bedford, Mass.
Lipson, Dr. Barnett, Los Angeles, Calif.
Liss, Dr. Edward, New York, N. Y.
Liswood, Dr. Rebecca, Brooklyn N. Y.
Litchfield, Dr. Harry R., Brooklyn, N. Y.
Litter, Dr. Leo, Hartford, Conn.
Litvak, Dr. Abraham, Brooklyn, N. Y.
Locke, Harry Dr., Hartford, Conn.
Lombard, Dr. J. Philip, Brooklyn, N. Y.
Lomant, Dr. Harry V., New York, N. Y.
London, Dr. William, Perth Amboy, N. J.
Loree, Dr. David R., Vancouver, Wash.
Louis, Dr. Marshall, Auburn, N. Y.
Lowe, Dr. C., Boston, Mass.
Lowenthal, Dr. Theresa, Canton, Mass.
Lowy, Dr. Moriz, New York, N. Y.
Lubitz, Dr. Thelma, Brooklyn, N. Y.
Ludlow, Dr. G. C., New Canaan, Conn.
Luhby, Dr. Leonard, Boston, Mass.
Luzzatti, Dr. Luigi, New York, N. Y.

Mabileau, Dr. Jean F., Washington, D. C.
MacDonald, Dr. Robert R., Pittsburgh, Pennsylvania.
MacFadden, Dr. Elbert F. Jr., Jamaica, N. Y.
Maclea, Dr. Margaret, Farmington, Conn.
Madden, Dr. Ethel M., Columbia, S. C.
Maddux, Dr. Walter H., Indianapolis, Indiana.
Magee, Dr. Conway, Lake Charles, La.
Maislen, Dr. Arthur A., Pittsfield, Mass.
Maksim, Dr. George, Washington, D. C.
Maliner, Dr. Martin M., Brooklyn, N. Y.
Mann, Dr. George V., Boston, Mass.
Manong, Dr. Stephen T., Niagara Falls, N. Y.
Marder, Dr. Signey S., Brooklyn, N. Y.
Margolis, Dr. Julius, Coatesville, Pa.
Marguis, Dr. Henrietta L., Charleston, W. V.
Marks, Dr. M. B., Miami Beach, Fla.
Markus, Dr. William B., Cleveland, Ohio.
Marotti, Dr. Rita C., Winter Haven, Fla.
Martin, Dr. Alexander Y., New York, N. Y.
Martin, Dr. Frederick J. Rochester, Rochester, N. Y.
Maslow, Dr. Herman L., Brooklyn, N. Y.
Mathiasen, Dr. Helena, Wappinger Falls, N. Y.
Matonis, Dr. Jos. F., Schuylkill Haven, Pa.
Matthews, Dr. Wallace R., Ashville, N. C.
Matthews, Dr. Wm. F., Montclair, N. J.
Mautner, Dr. Hans, Wrentham, Mass.
Mayhew, Dr. Fred, Rochester, Minn.
Mazo, Dr. Milton, Savannah, Ga.
Mazzoranna, Dr. Rafael Torres, Washington, D. C.
McAlenney, Dr. Paul F., New Haven, Conn.
McCain, Dr. Robert C., Chicago, Ill.
McCarthy, Dr. William C., Pittsburgh, Pa.
McCarthy, Dr. Frank W. Jr., Orangeburg, N. Y.
McCluskey, Dr. E. R., Pittsburgh, Pa.
McCoord, Dr. Augusta B., Rochester, N. Y.
McCormick, Dr. George W., Staten Island, N. Y.
McCoy, Dr. Bernice, Whittier, Calif.
McCrummen, Dr. Thomas D., Austin, Texas.
McCulloch, Dr. Hugh, St. Louis, Mo.
McCune, Dr. Donovan J., New York, N. Y.
McDonald, Dr. Francis C., Concord, Mass.
McElhenney, Dr. Tom J., Austin, Texas.
McGuinness, Dr. Aiks C., Philadelphia, Pa.
McIntosh, Dr. Rustin, New York, N. Y.

McKee, Dr. Margaret Harper, New York, N. Y.
McKee, Dr. Thistle W., Alexandria, Va.
McKhann, Dr. Charles F., Cleveland, Ohio.
McNamara, Dr. Frank,
McLendon, Dr. Preston A., Washington, D. C.
McQuarrie, Dr. Irvin, Minneapolis, Minn.
Medoff, Dr. H., New York, N. Y.
Mehrling, Dr. John H., Brooklyn, N. Y.
Melinek, Dr. Theodore, Philadelphia, Pa.
Merola, Dr. Edwin F., Waukegan, Ill.
Merritt, Dr. Katherine K., New York, N. Y.
Merrmann, Dr. Alan C., New York, N. Y.
Metzger, Dr. Harry C., Detroit, Mich.
Metrick, Dr. Bessie, New York, N. Y.
Meyer, Dr. Paul R., Port Arthur, Texas.
Meyer, Dr. Fritz M., Bridgeport, Conn.
Meyer, Dr. Henry S., Houston, Tex.
Meyer, Dr. Karl, New York, N. Y.
Meyer, Dr. Max, New York, N. Y.
Meyer, Dr. Selma Evelyn, Kew Gardens, N. Y.
Millard, Dr. Allen, Marshfield, Wisconsin.
Miller, Dr. Eleana, New York, N. Y.
Miller, Dr. John Fleek, Newark, Ohio.
Miller, Dr. Julius Y., Boston, Mass.
Miller, Dr. Philip R., Brooklyn, N. Y.
Mills, Dr. Stephen Dow, Westfield, N. J.
Minkowski, Dr. Alex, Boston, Mass.
Mitchell, Dr. F. Thos., Memphis, Tenn.
Mitchell, Dr. Harold H., New York, N. Y.
Mitchell, Dr. Reginald H., Bethesda, Md.
Mittelman, Dr. H. M., Scranton, Pa.
Moffett, Dr. Rudolph D., New York, N. Y.
Mohn, Dr. James F., Buffalo, N. Y.
Molnar, Dr. Julius, New York, N. Y.
Moloshok, Dr. Ralph E., New York, N. Y.
Monfort, Dr. John A., Brooklyn, N. Y.
Mongeau, Lorene, Wichita, Kans.
Montag, Dr. Leonard, Santa Monica, Calif.
Montague, Dr. J. Allison, New York, N. Y.
Montgomery, Dr. John C., Detroit, Mich.
Moore, Dr. Dorothea May, Cambridge, Mass.
Moore, Dr. J. Leonard, Princeton, N. J.
Morris, Dr. Paul, Philadelphia, Pa.
Morris, Dr. C. C., New Haven, Conn.

- Morrison, Dr. H. J., Savannah, Ga.
Mortimer, Dr. Edna Z., Joliet, Ill.
Mosher, Dr. T., New York, N. Y.
Mosse, Dr. Hilde Lachmann, New York, N. Y.
Motley, Dr. Hurley, New York, N. Y.
Mullen, Dr. F. N. Jr., Norfolk, Va.
Muniz, Dr. R. R., New York, N. Y.
Munro, Dr. Jeannette, Princeton, N. J.
Murray, Dr. Howard A., Newark, N. J.
Murray, Dr. Marjorie F., Cooperstown, N. Y.
Mustard, Dr. Harry, Durham, N. C.
Murphy, Dr. M. Lois, Philadelphia, Pa.
- Nauen, Dr. Alice, Cambridge, Mass.
Naumburg, Dr. Margaret, New York, N. Y.
Neal, Dr. E. Berkeley, Roanoke, Va.
Nebel, Dr. B. R., Geneva, N. Y.
Neborsky, Dr. Helen, New York, N. Y.
Neill, Philip B., Pittsburgh, Pa.
Nelson, Dr. Waldo E., Philadelphia, Pa.
Nemir, Dr. Rosa Lee, Brooklyn, N. Y.
Neuhaus, Dr. Hugo, Freeport, N. Y.
Neuland, Dr. William, New York, N. Y.
Neuman, Dr. K. G., Schenectady, N. Y.
Newman, Dr. Benjamin, Brooklyn, N. Y.
Nicholson, Dr. Margaret Mary, Washington, D. C.
Nicholson, Dr. Mary Virginia, Charlottesville, Va.
Nicholson, Dr. Percival, Ardmore, Pa.
Nicolson, Dr. Gertrude, New York, N. Y.
Nichtern, Dr. Sel, New York, N. Y.
Nicosia, Dr. Arnold Paul, New York, N. Y.
Nixon, Dr. Norman, New York, N. Y.
Nuila, Dr. Buenaventura, New York, N. Y.
- Obrinsky, Dr. William, New York, N. Y.
Odonnell, Dr. Francis T., Wilkes-Barre, Pa.
O'Donovan, Dr. C. J., Jersey City, N. J.
Ogden, Dr. Faith N., Norwalk, Conn.
O'Neal, Dr. Margaret, Zanesville, Ohio.
Oppenheimer, Dr. Ernest, Summit, N. J.
Orange, Dr. Michael, Brooklyn, N. Y.
O'Regan, Dr. C. H., New York, N. Y.
Orlofsky, Dr. Irene A., New York, N. Y.
Orr, Dr. William J., Buffalo, N. Y.
Osborn, Dr. John J., New York, N. Y.

Ostlund, Dr. Elvira, Rye, N. Y.
Outlar, Dr. L. B., Wharton, Texas.
Overton, Dr. David F., Newburgh, N. Y.
Owens, Dr. William W., Brooklyn, N. Y.

Pakula, Dr. Sidney F., Kansas City, Mo.
Palinsky, Dr. Max, Brooklyn, N. Y.
Palmieri, Dr. I., Brooklyn, N. Y.
Pappenheimer, Dr. A. M. Jr., New York, N. Y.
Park, Dr. Edwards A., Baltimore, Md.
Paul, Dr. R. M., Baltimore, Md.
Pawsat, Dr. E. H., Fond du Lac, Wisconsin.
Pearlman, Dr. Irving S., Brooklyn, N. Y.
Peck, Dr. Eleanor K., Poughkeepsie, N. Y.
Pennington, Dr. Katherine, Wichita, Kansas.
Perillo, Dr. Peter A., New York, N. Y.
Perman, Dr. Joshua M., Baltimore, Md.
Peters, Dr. Ella L., Boston, Mass.
Peters, Dr. J. T., New York, N. Y.
Peyton, Dr. Sarah M., Crisfield, Md.
Phillipe, Dr. Robert, New York, N. Y.
Phillips, Dr. John R., Allentown, Pa.
Phillips, Dr. W. R., Elmira, N. Y.
Piccoli, Dr. Leonard I., New York, N. Y.
Pierce, Dr. Nula I., Chicago, Ill.
Pinecock, Dr. Carolyn S., Washington, D. C.
Pineus, Dr. Joseph B., Brooklyn, N. Y.
Piserchia, Dr. Gerald J., Philadelphia, Pa.
Pizitz, Dr. Frances, New York, N. Y.
Platou, Dr. Ralph V., New Orleans, La.
Polk, Dr. D. Stewart, Rosemont, Pa.
Pollack, Dr. Roy, Cliffside Park, N. J.
Pollak, Dr. Rudolf, New York, N. Y.
Poncher, Dr. Henry G., Chicago, Ill.
Posner, Dr. David J., Brooklyn, N. Y.
Potter, Dr. Edith L., Chicago, Ill.
Potts, Dr. Willis J., Oak Park, Ill.
Powell, Dr. Ethel B., Long Beach, Calif.
Prentice, Dr. Stanley L., Brooklyn, N. Y.
Previtali, Dr. Giuseppe, New York, N. Y.
Prigosen, Dr. Rosa E., Brooklyn, N. Y.
Prince, Dr. George E., Gastonia, N. C.
Proctor, Dr. Donald F., Baltimore, Md.
Pyle, Dr. Idell, Cleveland, Ohio.

Quilligan, Dr. Frank J.,
Quimby, Dr. Edith H., New York, N. Y.
Quinn, Dr. C. Bernardin, Jenkintown, Pa.
Quinn, Dr. Thomas R., Pittsburgh, Pa.

Rabe, Dr. Edward F., New Haven, Conn.
Rabinoff, Dr. Sophie, New York, N. Y.
Rabnowitz, Dr. Henry, Brocton, Mass.
Race, Dr. Oscar M., Staten Island, N. Y.
Raffetto, Dr. Joseph F., Asbury Park, N. J.
Ragan, Dr. C. A., New York, N. Y.
Randall, Dr. John A., Staten Island, N. Y.
Randol, Dr. Charles Lee, Baltimore, Md.
Rapaport, Dr. Howard G., New York, N. Y.
Rascoff, Dr. Henry, Brooklyn, N. Y.
Ratner, Dr. Bret, New York, N. Y.
Ravin, Dr. Nathan, New York, N. Y.
Ray, Dr. Pauline, New York, N. Y.
Read, Dr. Frances E. M., Baltimore, Md.
Rednor, Dr. Bernard, New York, N. Y.
Reed, Dr. Donald R., Tarrytown, N. Y.
Reifenstein, Dr. Edward C. Jr., New York, N. Y.
Reiner, Dr. Miriam, New York, N. Y.
Reisman, Dr. Henry A., New York, N. Y.
Repici, Dr. Anthony J., Hammonton, N. J.
Reynolds, Dr. Margaret, Jackson Heights, N. Y.
Rhea, Dr. James W., New York, N. Y.
Richardson, Dr. Mary L., Philadelphia, Pa.
Rice, Dr. J. B., New York, N. Y.
Rie, Dr. G. A.,
Rie, Dr. M. L.,
Rie, Dr. George A., New York, N. Y.
Riley, Dr. Conrad M., New York, N. Y.
Ritchie, Dr. Jean A. S., Washington, D. C.
Robbins, Dr. Anne S., Dayton, Ohio.
Roberts, Dr. Dudley, New York, N. Y.
Robinson, Dr. Arthur, New York, N. Y.
Robinson, Dr. Irving W., New York, N. Y.
Roddy, Dr. R. L., Jenkinstown, Pa.
Rogatz, Dr. Julian L., New York, N. Y.
Roscoe, Dr. Constantine, Philadelphia, Pa.
Rose, Dr. Elizabeth Kirk, Philadelphia, Pa.
Rosen, Dr. Alexander S., Great Neck, N. Y.
Rosenberg, Dr. Albert A., Poughkeepsie, N. Y.

- Rosenberg, Dr. Philip, Syracuse, N. Y.
Rosenberg, Dr. Albert, A. Swainsboro, Ga.
Rosenberg, Dr. H., New York, N. Y.
Rosenblum, Dr. Jacob, Brooklyn, N. Y.
Rosenfeld, Dr., New York, N. Y.
Rosenson, Dr. William, New York, N. Y.
Rosenthal, Dr. Karl, New York, N. Y.
Rosenthal, Dr. Stephan I., Scranton, Pa.
Ross, Dr. Daniel, Staten Island, N. Y.
Roth, Dr. Carolyn B., Cincinnati, Ohio.
Rothbard, Dr. Mary Boon, New York, N. Y.
Rousseau, Dr. Paul, New York, N. Y.
Rove, Dr. Simon, Kew Gardens, N. Y.
Rubenstein, Dr. Flora K., Brooklyn, N. Y.
Rubin, Dr. Harold S., Hempstead, N. Y.
Rubin, Dr. Mitchell E., Buffalo, N. Y.
Rubenstein, Dr. Allan A., Laurelton, L. I., N. Y.
Rubinstein, Dr. Benjamin, Brooklyn, N. Y.
Rubinstein, Dr. Mina, Brooklyn, N. Y.
Rudd, Dr. Lucie, New York, N. Y.
Rudomanski, Dr. Victor, Kearny, N. J.
Russell, Dr. James Earl Jr., Denver, Colo.
Rutherford, Dr. Robert T. Jr., Alexandria, Va.
- Sabin, Dr. Albert, B., Cincinnati, Ohio.
Sachs, Dr. Benjamin, Hartford, Conn.
Saltiel, Dr. Thomas P., Chicago, Ill.
Sanders, Dr. O. Perdue, Dallas, Tex.
Scharf, Dr. Albert, New York, N. Y.
Scheer, Dr. Cire, Seattle, Wash.
Scheer, Dr. Eli, Teaneck, N. J.
Scheffrin, Dr. Alec E., Passaic, N. J.
Schick, Dr. Bela, New York, N. Y.
Schiff, Dr. Erwin, New York, N. Y.
Schildkrout, Dr. Mollie, New York, N. Y.
Schley, Dr. Frank B., Columbus, Ga.
Schley, Jr., Dr. Richard L., Savannah, Ga.
Schloss, Dr. Lewis J., New York, N. Y.
Schmidt, Dr. Albert, Sea Girt, N. J.
Schmidt, Charlotte, New York, N. Y.
Schneider, Dr. Linda T., Cleveland, Ohio.
Scholz, Dr. Pearl Huffman, Baltimore, Md.
Schorer, Dr. Edwin, Kansas City, Mo.
Schubert, Dr. Agnes, New York, N. Y.

Schwartz, Dr. Oscar, Brooklyn, N. Y.
Schwartz, Dr. Robert, New York, N. Y.
Schwarz, Dr. Edwin G., Ft. Worth, Texas.
Schwentker, Dr. Francis F., Baltimore, Md.
Scobey, Dr. Ralph R., Syracuse, N. Y.
Scott, Dr. John Porter, Philadelphia, Pa.
Scott, Dr. T. F. McNair, Philadelphia, Pa.
Scott, Dr. Caroline P., Lexington, Ky.
Seoville, Dr. Dorothea H., Richmond, Calif.
Searle, Dr. Donald S., New York, N. Y.
Sedam, Dr. Margaret Soars, Redlands, Calif.
Seegal, Dr. Beatrice Carrier, New York, N. Y.
Selinger, Dr. Bernard, Glens Falls, N. Y.
Senn, Dr. Milton J. E., New York, N. Y.
Shafer, Dr. Charles L., Mansfield, Ohio.
Sharp, Dorothy, J., Brooklyn, N. Y.
Shapiro, Dr. Andrew D., Roanoke, Va.
Shapiro, Dr. Irene, New York, N. Y.
Shapiro, Dr. Lawrence M., New York, N. Y.
Sherlin, Dr. Charles F., New York, N. Y.
Sherman, Dr. M., Brooklyn, N. Y.
Sherman, Dr. Rose, New York, N. Y.
Sherman, Dr. Harry, Brooklyn, N. Y.
Shields, Dr. Walter J., Brooklyn, N. Y.
Shimmerlik, Dr. Lucy, New York, N. Y.
Shinefield, Dr. Maurice A., Paterson, N. J.
Shuler, Dr. Virginia, Chicago, Ill.
Shuman, Dr. H. H., Springfield, Mass.
Sidbury, Dr. J. Buren, Wilmington, N. C.
Siegel, Dr. Erieh, New York, N. Y.
Sigel, Dr. M. M., Philadelphia, Pa.
Silberbush, Dr. F., Brooklyn, N. Y.
Silberman, Dr. Norman, New York, N. Y.
Silver, Dr. Francis, Cleveland Hts., Ohio.
Silverman, Dr. A. Clement, Syracuse, N. Y.
Silverman, Dr. Frederic, New York, N. Y.
Simmons, Dr. R. N.,
Sinecock, Dr. H. A., Superior, Wis.
Sisson, Dr. Warren R., Boston, Mass.
Skirball, Dr. Louis I., Boston, Mass.
Slack, Dr. Louise, W. Lancaster, Pa.
Slater, Dr. Beatrice S., New York, N. Y.
Small, Dr. Leon I., Brooklyn, N. Y.
Smith, Dr. Alan E., Stewartstown, Pa.

Smith, Dr. Carl H., New York, N. Y.
Smith, Dr. Clement A., Boston, Mass.
Smith, Dr. Marjorie K., Longview, Wash.
Smith, Dr. Norman, New York, N. Y.
Smith, Dr. Robert, New York, N. Y.
Smith, Dr. Richard M., Boston, Mass.
Smith, Dr. Wm. Russell,
Smith, Dr. C. A., Petoskey, Mich.
Snaith, Dr. Theresa O., Weston, W. Va.
Snedeker, Dr. Lendon, Brookline, Mass.
Snidely, Dr. W. D., Evansville, Ind.
Snyderman, Dr. Selma E., New York, N. Y.
Sobel, Dr. A. E., Brooklyn, N. Y.
Socola, Dr. Edwin A., New Orleans, La.
Sommer, Dr. Otto, Mt. Vernon, N. Y.
Sommers, Dr. Raymond L., Rochester, N. Y.
Soule, Dr. H. C., New York, N. Y.
Souther, Dr. Martha C., Indianapolis, Ind.
Spahr, Dr. Mary B., Ithaca, N. Y.
Spickard, Dr. Vernon W., Seattle, Wash.
Spigel, Dr. Harry A., Washington, D. C.
Spiegel, Dr. Rose G., New York, N. Y.
Spier, Dr. Patricia E., New York, N. Y.
Spiro, Dr. L., Washington, D. C.
Stafford, Dr. Henry E., Vallejo, Calif.
Standard, Dr. Ruth, Silver Spring, Md.
Stare, Dr. Frederick J., Boston, Mass.
Starr, Dr. Saul, Brooklyn, N. Y.
States, Miss Virginia, New York, N. Y.
Statell, Dr. Pasquale, Jersey City, N. J.
Stearns, Dr. Genevieve, Iowa City, Iowa.
Steigerwalt, Dr. Mildred, New York, N. Y.
Stein, Dr. Eleanor Robb, Harrisburg, Pa.
Stein, Dr. Joseph, Jamaica, N. Y.
Steiner, Dr. Morris, Brooklyn, N. Y.
Stevenson, Dr. J. D., Beaver, Pa.
Stewart, Dr. Alexander, St. Paul, Minn.
Stewart, Dr. Colin C., Hanover, N. H.
Stewart, Dr. Walter B., Atlantic City, N. J.
Stigliano, Dr. Anthony Gerard, Brooklyn, N. Y.
Stiles, Dr. David, New York, N. Y.
Stillerman, Dr. Maxwell, Great Neck, N. Y.
Stimson, Dr. Philip M., New York, N. Y.
Stitt, Dr. Donald G., Philadelphia, Pa.

- Stoecklein, Dr. Christian J., Pittsburgh, Pa.
Stoerk, Dr. Herbert C., Boston, Mass.
Stokes, Dr. Joseph Jr., Philadelphia, Pa.
Stokes, Dr. Joseph III, Philadelphia, Pa.
Strayer, Dr. Edward B., Philadelphia, Pa.
Stringfield, Dr. Oliver L., Stamford, Conn.
Strongin, Dr. H., Brooklyn, N. Y.
Stuart, Dr. Harold C., Boston, Mass.
Stuckey, Dr. Anne D., Griffin, Ga.
Studder, Dr. John, New York, N. Y.
Strupp, Dr. Charlotte W., Bronxville, N. Y.
Sugarman, Dr. Jacob, New York, N. Y.
Sullivan, Dr. Alma M., New Orleans, La.
Sullivan, Dr. Albert W., New York, N. Y.
Suskind, Dr. Elizabeth, New York, N. Y.
Susman, Dr. Abraham B., New York, N. Y.
Sutton, Dr. Lee E. Jr., Richmond, Va.
Sykes, Dr. Robert Hart, Geneva, Ill.
Scanton, Dr. Victor L., Jackman, Maine.
Szelewa, Dr. Edward, Newark, N. J.
Szulberg, Dr. Brona, New York, N. Y.
- Tamagnam, Dr. Irene G., New York, N. Y.
Tang, Dr. I. Ling, Rochester, N. Y.
Tappan, Dr. Vivian, Tuscon, Arizona.
Tarre, Dr. Harold I., New York, N. Y.
Taylor, Dr. Grant, Durham, N. C.
Temerson, Dr. Henri, New York, N. Y.
Tepper, Dr. Clifford A., Brooklyn, N. Y.
Thompson, Dr. Helen, New York, N. Y.
Thompson, Dr. K. W., Nutley, N. J.
Tinsley, Dr. John C., St. Louis, Mo.
Toller, Dr. Else, Croton-on-Hudson, N. Y.
Tomson, Dr. Irene, New York, N. Y.
Toomey, Dr. John A., Cleveland, Ohio.
Topper, Dr. Anne, New York, N. Y.
Torres, Dr. Francisco E., Indianapolis, Ind.
Tow, Dr. Abraham, New York, N. Y.
Townsend, Jr., Dr. Edward H., New York, N. Y.
Towsley, Dr. Harry A., Ann Arbor, Mich.
Trainham, Dr. A. Genevieve, Detroit, Mich.
Tytko, Dr. M. J., Schenectady, N. Y.
- Ufford, Dr. Elizabeth, Port Washington, N. Y.
Ungaro, Dr. Harold, New York, N. Y.

Unna, Dr. Maya S., Bellwood, Ill.

Untracht, Dr.

Utz, Dr. David W., Rockville Center, N. Y.

Van Alk, Dr. Bert, Eaton Rapids, Mich.

Vandam, Dr. Leroy, Baltimore, Md.

Van Gelden, Dr. David W., Baton Rouge, La.

Van Horn, Dr. A. L., Washington, D. C.

Vann, Dr. Dorothea, Englewood, N. J.

Van Riper, Dr. Hart E., New York, N. Y.

Varden, Dr. Arthur E., San Bernardino, Calif.

Vaughan, Dr. Victor C., Boston, Mass.

Vechsler, Dr. Marc, New York, N. Y.

Veeder, Dr. Borden S., St. Louis, Mo.

Venegas, Dr. Francisco, Rochester, Minn.

Venning, Dr. W. L., Charlotte, N. C.

Ver, Dr. Katherine, Dayton, Ohio.

Vergara, Dr. Arturo, Washington, D. C.

Vilnel, Dr. Alfred J., New York, N. Y.

Vollmer, Dr. Herman, New York, N. Y.

Voong, Dr. Stephan, Staten Island, N. Y.

Vosburgh, Dr. Gilbert J., Baltimore, Md.

Wachtell, Dr. Sidney, New York, N. Y.

Wade, Dr. George, Philadelphia, Pa.

Wagner, Dr. Elizabeth Martin, Chicago, Ill.

Wagner, Dr. Richard, Boston, Mass.

Wakeman, Dr. E. T., New Haven, Conn.

Waldinger, Dr. Clara, Boston, Mass.

Walker, Dr. Lillie Cutler, Asheville, N. C.

Walker, Dr. Thomas B., Portsmouth, N. H.

Wallace, Dr. Helen M., New York, N. Y.

Wallace, Dr. Wm. M., Boston, Mass.

Wannamaker, Dr. Lewis, New York, N. Y.

Ward, Dr. Robert, New York, N. Y.

Ward, Dr. Richard, New York, N. Y.

Ward, Dr. Thomas G., Baltimore, Md.

Warkany, Dr. Josef, Cincinnati, Ohio.

Warner, Dr. Robert, Cincinnati, Ohio.

Warren, Dr., New York, N. Y.

Warshall, Dr. Hyman B., Brooklyn, N. Y.

Watson, Ernest S., Elmhurst, Ill.

Watton, Dr. Walter F., Brooklyn, N. Y.

Weber, Dr. Mortimer W., New York, N. Y.

Weber-Escherich, Dr. Soiya, Mt. Vernon, N. Y.
Wedgwood, Dr. Ralph, New York, N. Y.
Wegman, Dr. M. E., New Orleans, La.
Weichsel, Dr. Manfred, New York, N. Y.
Weinstock, Dr. Irving, Brooklyn, N. Y.
Weintraub, Dr. David H., Buffalo, N. Y.
Weiss, Dr. Gertrud, New York, N. Y.
Weissberg, Dr. William W., New York, N. Y.
Welford, Dr. Norman T., La Orange, Ill.
Wellmeier, Dr. Hugh, Piqua, Ohio.
Wells, Dr. Jean, West Hartford, Conn.
Wells, Dr. Beulah, Cleveland, Ohio.
Welner, Dr. Daniel, New York, N. Y.
Wendell, Dr. K., Philadelphia, Pa.
Wershof, Dr. Stanley M., New York, N. Y.
West, Dr. Joseph R., New York, N. Y.
West, Dr. Robert, New Rochelle, N. Y.
Wexler, Dr. Irving B., Brooklyn, N. Y.
Weyland, Dr. Charletta K., Lebanon, Pa.
Weymuller, Dr. Charles A., Brooklyn, N. Y.
Whalen, Dr. Edward P., Ogdensburg, N. Y.
Wheatley, Dr. George M., New York, N. Y.
Whipple, Dr. Dorothy V., Arlington, Va.
White, Dr. Leta J., Petersburg, Va.
Whittemore, Dr. James, New York, N. Y.
Whittemore, Dr. Ruth, Baltimore, Md.
Wiener, Dr. Alex. S., Brooklyn, N. Y.
Wiener, Dr. Harry, Washington, D. C.
Wier, Dr. Edward, Ft. Worth, Texas.
Wiese, Dr. Hilda F., Galveston, Texas.
Wilens, Dr. Gustav, Wayland, Mass.
Wilens, Dr. Catherine W., Wayland, Mass.
Wilhelm, Dr. Hazel S., New York, N. Y.
Wilke, Dr. Frederick H., New York, N. Y.
Wilkes, Dr. Edward T., Long Island City, N. Y.
Williams, Dr. W., New York, N. Y.
Williamson, Dr. Carolyn G., Orlando, Fla.
Wilkes, Dr. Frederick B., Buffalo, N. Y.
Wilkins, Dr. Lawson, Baltimore, Md.
Williams, Dr. Herbert M., Kew Gardens, N. Y.
Wilson, Dr. May G., New York, N. Y.
Wilson, Dr. Sampson J., Brooklyn, N. Y.
Winograd, Dr. Abbott L., Lynn, Mass.
Witebsky, Dr. Ernest, Buffalo, N. Y.

Withers, Dr. Martin S., Los Alamos, New Mexico.
Wolfe, Dr. S. George, Shreveport, La.
Wolman, Dr. Irving J., Philadelphia, Pa.
Wolpe, Dr. Leon Z., Beverly Hills, Calif.
Wong, Dr. Edward, New York, N. Y.
Wong, Dr. Helena, Boston, Mass.
Wong, Dr. Virginia, New York, N. Y.
Wood, Dr. I. Robert, New York, N. Y.
Worcester, Dr. Blandina, New York, N. Y.
Worthington, Dr. Dorothy, White Plains, N. Y.
Wright, Dr. P., New York, N. Y.
Wylde, Dr. M. K., Albuquerque, New Mexico.
Wynkoop, Dr. Edward J., Syracuse, N. Y.

Yarow, Dr. Natalie, New York, N. Y.

Zamkin, Dr. Harry D., New York, N. Y.
Zannos, Dr. Leda, New York, N. Y.
Zelson, Dr. Carl, New York, N. Y.
Zininger, Dr. Pauline, Canton, Ohio.
Ziön, Dr. Lena, Brooklyn, N. Y.
Zipser, Dr. Stanley S., New York, N. Y.

Monday, 14th July.

Meeting of the National Committees.

Meeting of the National Committees was held on Monday, July 14, 1947.

The first order of business was the election of a member of the Congress to respond for the fifty-six nations. Doctor Robert Debré of Paris, France, was unanimously elected.

The second order of business was the selection of a place to hold the Sixth International Congress of Pediatrics. Doctor Fanconi presented Switzerland's invitation and by unanimous vote it was decided to hold the next Congress in Switzerland. Doctor Fanconi was nominated as President; the nomination was seconded; as there were no further nominations the secretary was asked to cast the ballot for Doctor Fanconi. He was elected.

The third order of business was the matter of changes in the constitution. After considerable discussion regarding the interrupted nature of the Congress and the importance of establishing firmer international relationships, it was decided to add to paragraph one that there shall be elected a permanent secretary of the International Pediatric Association. The president then asked for nominations for this office of permanent secretary. Doctor Hurtado of Cuba nominated Doctor L. Emmett Holt, Jr. There were no further nominations. On motion, the secretary cast the ballot. Doctor L. Emmett Holt, Jr. was elected to the position of permanent secretary. To still further help to give permanency and continuity to any program a motion that a committee of seven be appointed to act for the next three years was made. This committee was to be appointed by the incoming president. This motion to establish such a committee was duly seconded and carried. Doctor Fanconi appointed the following committee:

Doctor Robert Debré of France, Doctor Mikhail C. Maslov of Russia, Doctor Federigo Gomez of Mexico, Doctor Alan Moncrieff of Great Britain, Doctor L. Emmett Holt, Jr. of the United States, and Doctor Henry F. Helmholtz of the United States with Doctor Fanconi as chairman.

A statement was read regarding the International Childrens Emergency Fund. A motion that the Fifth International Congress of Pediatrics approve in principle the aims and objectives of the United Nations program in the aid of children was made, seconded and unanimously adopted.

Program.

Tuesday, July 15.

Plenary Session — Nutrition.

Relators:

Prof. R. A. McCANCE, Department of Experimental Medicine,
Cambridge, England.

Dr. J. H. P. JONXIS, Rotterdam, Netherlands.

Co-relators:

Dr. JOSEPH GILLMAN, University of the Witwatersrand, Johannesburg, Union of South Africa.

Prof. P. PLUM, Director of the Pediatric Division, Rigshospital, Copenhagen, Denmark.

Dr. GEORGE LOGARAS, Athens, Greece.

Dr. DAG RIIS, Municipal Bureau of Maternal and Child Welfare, Oslo, Norway.

Discussion:

Dr. K. C. CHAUDHURI, Editor of the Indian Journal of Pediatrics, Calcutta, India.

Prof. M. S. MASLOFF, Academy of Medical Science, Leningrad, U. S. S. R.

Prof. C. B. CHOREMIS, Athens, Greece.

Dr. PETER V. VÉGHÉLYI, Pediatric Department of the Budapest University, Budapest, Hungary.

Dr. A. V. S. SARMA, Honorary Physician, Government Royafettah Hospital, Madras, India.

Wednesday, July 16.

Plenary Session — Diseases Caused by Filterable Viruses.

Relator, Neurotropic Viruses:

Dr. ALBERT B. SABIN, Children's Hospital Research Foundation, Cincinnati, Ohio, U. S. A.

Discussion:

Dr. LESLIE ALM, Bacteriological Laboratory, Sahlgren Hospital, Gothenburg, Sweden.

Prof. HAROLD K. FABER, Stanford University School of Medicine, San Francisco, California, U. S. A.

Relator, Respiratory Viruses:

Prof. THOMAS FRANCIS, JR., University of Michigan School of Public Health, Ann Arbor, Michigan, U. S. A.

Discussion:

Dr. JOHN M. ADAMS, Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota, U. S. A.

Prof. CHARLES A. JANEWAY, Harvard University Medical School, Boston, Massachusetts, U. S. A.

Plenary Session — Chemotherapy of Infectious Diseases.*Relator:*

Prof. CHESTER S. KEEFER, Evans Memorial Hospital, Boston, Massachusetts, U. S. A.

Co-relators:

Prof. GINO FRONTALI, University of Rome, Rome, Italy.

Prof. RUDOLF DEGKWITZ, University Children's Clinic, Hamburg, Germany.

Discussion:

Dr. ANDOR BOSÁNYI, St. László Hospital for Infectious Diseases, Budapest, Hungary.

Dr. MANUEL SUÁREZ PERDIGUERO, University of Zaragoza, Zaragoza, Spain.

Prof. W. S. GAISFORD, Manchester, England.

Plenary Session — Neonatal Mortality.*Relator:*

Prof. ALAN MONCRIEFF, Hospital for Sick Children, Great Ormond Street, London, England.

Co-relators:

- Prof. CURT GYLLENSWÄRD, University of Uppsala, Uppsala, Sweden.
Prof. Dr. AUGUST REUSS, Vienna, Austria.

Discussion:

- Dr. ALEKSANDRA KUROWSKA, Children's Clinic, Poznań University, Poznań, Poland.
Dr. JULIO A. BAUZÁ, Presidente del Consejo del Niño, Montevideo, Uruguay.
Dr. A. F. TOUR, Children's Institute, Leningrad, U. S. S. R.

Sectional Meetings.**Section 1: Factors in Pregnancy Affecting the Child.**

- Dr. LORIMER DODS, Royal Alexander Hospital for Children, Sydney, Australia. — Maternal Rubella as a Cause of Congenital Defects in Infancy.
Dr. J. HARRY EBBS, Hospital for Sick Children, Toronto, Canada. — The Effect of Prenatal Nutrition on the Mother and Child.
Prof. M. LAMY, Hôpital des enfants malades, Paris, France. — Notes cliniques sur un cas d'enfant du radium.
Dr. GEORG LENART, Stephanie Children's Hospital, Budapest, Hungary. — Jaundice and Blood Groups.
Dr. SP. CHAROKOPOS, Kyriakou Children Hospital, Athens, Greece. — Rh-factor in children diseases.
Dr. ELIAS HALAC, Prof. A. de Pediatría de la Fac. de Medicina y Director de la Escuela de Puericultura de Córdoba. — Isoimmunización por el factor Rh. Estudio sobre su duración en estado activo.
Dr. JOSEF WARKANY, Children's Hospital Research Foundation, Cincinnati, Ohio, U. S. A. — Congenital Malformations Induced in Rats by Maternal Nutritional Deficiency.
Dr. HOLGER DYGGVE, University Lying-In Department, Copenhagen, Denmark. — The Value of Administration of Synthetic Vitamin K before Labor.

Section 2: Preventive Pediatrics.

- Prof. Dr. HENRYK BROKMAN, Akademia Lekarska, Gdańsk, Poland. — Les maladies causées par le groupe *Salmonella* en rapport avec les diarrhées saisonnières chez les enfants.
- Dr. YUNG-EN KAO, National Kwei-yang Medical College, Kweichow, China. — Breast Feeding in China.
- Prof. A. LICHTENSTEIN, Kronprinsessan Lovisas Children's Hospital, Stockholm, Sweden. — Preventive Pediatrics in Sweden.
- Dr. JESÚS LOZOYA S., Hospital del Niño, Mexico City, Mexico. — Pediatric Surgery in Mexico.
- Dr. A. F. TOUR, Children's Institute, Leningrad, U. S. S. R. — Protection de la santé des enfants en U. R. S. S.
- Dr. KIRSTEN UTHEIM TOVERUD, Municipal Bureau of Maternal and Child Welfare, Oslo, Norway. — Results of a Systematic Health Program for Mothers and Children in Oslo during the War.
- Prof. ARVO YLPPÖ, Children's Clinic, Helsinki, Finland. — The Construction of a Modern Children's Clinic.

Section 3: Bio-Immunological Procedures.

- Dr. BO VAHLQUIST, Norrtulls Sjukhus, Stockholm, Sweden. — Immunization against Diphtheria in Newborn Babies and Infants.
- Prof. FRANCISZEK GROËR, Cracow, Poland. — A New Approach to the Problem of Diphtheria.
- Dr. LÉONE MARYSSAEL, Brussels, Belgium. — Une nouvelle réaction pour la recherche des sujets réceptifs à la diphtérie.
- Dr. SP. CHARACOPOS, Children Clinic of Athens University, Athens, Greece. — The Relation of the Types of *Corynebacterium Diphtheriae* to Diphtheria.
- Prof. JAROSLAV PROCHÁZKA, Karlova University, Prague, Czechoslovakia. — The Prophylaxis of Acute Anterior Poliomyelitis.
- Dr. CHARLES WALTNER, Budapest, Hungary. — Autophyotherapy of Acute Hematogenous Osteomyelitis.

Section 4: Vitamin Requirements and Avitaminoses.

Dr. SOTIRIOS BRISKAS, Hôpital des enfants malades, Paris, France. — Troubles de la croissance chez l'enfant par doses massives de vitamine D 2.

Dr. MAMDOOH HANAFY, Farouk 1st University Faculty of Medicine, Alexandria, Egypt. — The Subacute Subnutritional Syndrome in Infants.

Dr. J. G. PAGOLA, Hospital del Niño, México D. F., Mexico. — Avitaminosis in Mexico; a Study of Five Hundred Cases.

Prof. S. VAN CREVELD, University of Amsterdam, Amsterdam, Netherlands. — Avitaminosis in Dutch Children in Concentration Camps.

Prof. E. ROMINGER, University Children's Clinic, Kiel, Germany. — Citric Acid and Rickets.

Section 5: Insect and Other Vectors of Disease.

Dr. S. BERMAN, Hadassah University Hospital, Jerusalem, Palestine. — Protozoal Diarrheas in Childhood.

Dr. RUSSELL J. BLATTNER, Washington University, St. Louis, Missouri, U. S. A. — The Epidemiology of St. Louis Encephalitis.

Prof. G. SALVIOLI, University of Bologna, Italy. — Sensitivity of Animals (Cats) to Epithelial Virus of Poliomyelitis.

Dr. HUA KANG CHOW, University of Minnesota Medical School, Minneapolis, Minnesota, U. S. A. — The Problem of Leishmaniasis (Kala Azar) in China.

Prof. ALBERT ECKSTEIN, University Children's Clinic, Ankara, Turkey. — Malaria im Kindesalter.

Section 6: Rheumatic Fever.

Dr. PAUL GIRAUD, Marseille, France. — La fièvre rhumatismale dans ses rapports avec les autres fièvres de nature allergique.

Dr. HELEN KAGAN, Bikur Cholim Hospital, Jerusalem, Palestine. — The Incidence of Rheumatic Fever in Jerusalem and the Beginnings of Chemoprophylaxis.

Dr. WILFRID SHELDON, Great Ormond Street Hospital, London, England. — Rheumatic Fever.

Dr. KENNETH TALLERMAN, London, England.

Prof. JOSÉ MARÍA MACERA, Buenos Aires, Argentina. — La enfermedad reumatica en la Republica Argentina.

Dr. KSAWERY LEWKOWICZ, Cracow, Poland. — Essential Notions on Tuberculo-Rheumatic Disease (T. R. D.).

Section 7: Endocrinology in Childhood.

Dr. SPYROS BARTSOCAS, Evangelismos Hospital, Athens, Greece.
— A propos d'un cas de virilisme surrénal avec tumeur de la corticale surrénale et diabète insipide chez une fillette de 28 mois.

Dr. A. L. CHUTE, Hospital for Sick Children, Toronto, Canada.
— The Late Complications of Juvenile Diabetes.

Dr. ROBERT CLÉMENT, Paris, France. — Le syndrome pseudo-basedowien de la puberté.

Prof. ROBERT DEBRÉ, University of Paris, Paris, France. — Nanisme avec oligodipsie.

Prof. R. W. B. ELLIS, University of Edinburgh, Edinburgh, Scotland. — Growth and Maturity of Boys in Relation to School-Leaving Age.

Dr. GEORG LENART, Stephanie Children's Hospital, Budapest, Hungary. — The Role of Non-Glandular Hormones in Differentiation and Growth.

Dr. O. D. SOKOLOVA-PONAMAROVA, Director of Pediatric Clinic, Omsk, U. S. S. R. — Endemic Goitre in Children.

Section 8: Miscellaneous Topics.

Dr. ROLF BERGMAN, Stockholm, Sweden. — Eight Hundred Cases of Poliomyelitis Treated in the Sahlin Respirator.

Dr. ZAIDA ERIKSSON-LIHR, Helsingfors, Finland. — The Treatment of Asthma Bronchiale in Children in Finland.

Prof. ERNST FREUDENBERG, University Children's Clinic, Basel, Switzerland. — The Importance of Kathepsin for the Protein Digestion in the Stomach.

- Dr. T. HALBERTSMA, Haarlem, Netherlands. — Gold Compounds in the Treatment of Chronic Arthritis in Children.
- Prof. MARCEL LELONG, University of Paris, Paris, France. — Le brachy-œsophage chez le nourrisson.
- Prof. R. A. McCANCE, Department of Experimental Medicine, Cambridge, England. — Some Recent Developments in our Knowledge of Renal Function in Infancy.
- Dr. PETER VÉGHÉLYI, Budapest University, Budapest, Hungary. — Pancreatic Function in Different Clinical Conditions.
- Dr. SVEN BRANDT, Aarhus, Denmark. — The Prognosis of Amyotonia Congenita.

Thursday, July 17.

Plenary Session — Tuberculosis.

Relators:

- Prof. ARVID J. WALLGREN, Royal Caroline Medical Institute, Stockholm, Sweden.
- Prof. K. JONSCHER, University Children's Hospital, Poznan, Poland.

Co-relators:

- Dr. ALBERTO CHATTÁS, Córdoba, Argentina.
- Prof. ROBERT DEBRÉ, University of Paris, Paris, France.
- Dr. J. H. HUTCHISON, Glasgow, Scotland.
- Prof. GERHARD WEBER, University Children's Clinic, Munich, Germany.

Discussion:

- Dr. LUIZ T. BARBOZA, Instituto Nacional de Puericultura, Rio de Janeiro, Brazil.
- Dr. ALBERT GUILBEAULT, B. C. G. Institute, Montreal, Canada.
- Dr. GIAN PIETRO RAVERA, Turin, Italy.
- Prof. CONSTANTINE CHOREMIS, Athens, Greece.
- Dr. M. WEILL-HALLÉ, Paris, France.
- Prof. A. F. TOUR, Children's Institute, Leningrad, U. S. S. R.
- Dr. L. DE CASTRO FREIRE, Lissabon, Portugal.

Prof. JOSE MARTINO DA ROCHA, Rio de Janeiro, Brazil.
Dr. SP. CHARACOPOS, Athens, Greece.
Dr. P. W. BRAESTRUP, Copenhagen, Denmark.
Dr. S. BRISKAS, Paris, France.
Prof. G. SALVIOLI, Bologna, Italy.
Dr. CAMILLE KERESZTURI CAYLEY, New York, U. S. A.

Plenary Session — Incompatibility of Blood.

Relator:

Prof. GIOVANNI DE TONI, University Children's Clinic, Genoa, Italy.

Co-relators:

Dr. BIRGER BROMAN, Royal Caroline Medical School, Stockholm, Sweden.
Dr. I. HALBRECHT, Tel-Aviv, Palestine.

Discussion:

Dr. BRUCE CHOWN, Children's Hospital, Winnipeg, Canada.
Dr. LOUIS K. DIAMOND, Children's Hospital, Boston, Massachusetts, U. S. A.
Sir LEONARD G. PARSONS, Birmingham, England.
Prof. ALDO MUGLIA, Quito, Ecuador.

Plenary Session — »Alimentary Toxicosis«.

Relator:

Prof. E. KERPEL-FRONIUS, University Children's Clinic, Pécs, Hungary.

Co-relators:

Prof. ANGEL A. ABALLÍ, Havana, Cuba.
Prof. LUDWIG F. MEYER, Tel-Aviv, Palestine.

Discussion:

Prof. GUIDO FANCONI, University Children's Clinic, Zürich, Switzerland.
Prof. EVERT GORTER, Leyden, Netherlands.

Prof. FÉLIX HURTADO, Havana, Cuba.

Dr. MAURICE LUST, Brussels, Belgium.

Dr. K. BIERING-SØRENSEN, Copenhagen, Denmark.

Plenary Session — Congenital Heart Disease.

Relator:

Dr. AUGUSTÍN CASTELLANOS, Havana, Cuba.

Co-relators:

Dr. EDGAR MANNHEIMER, Kronprinsessan Lovisas Children's Hospital, Stockholm, Sweden.

Dr. ANDRÉ Cournand, Bellevue Hospital, New York, N. Y., U. S. A.

Discussion:

Dr. R. AGUILAR, México, D. F., Mexico.

Prof. IVAN HECKO, Bratislava, Czechoslovakia.

Dr. JOHN D. KEITH, Hospital for Sick Children, Toronto, Canada.

Prof. MAURICE LAMY, Hôpital des enfants malades, Paris, France.

Tuesday, 15th July.

Addresses of Welcome.

By **Henry F. Helmholtz**, President:—

At this the opening session of the Fifth International Congress of Pediatrics, it is my great privilege to extend to you all the very warmest welcome on behalf of the American Academy of Pediatrics, the American Pediatric Society, the Pediatric Section of the American Medical Association, and the Society for Pediatric Research.

To have this large representative group of pediatricians from the four corners of the world here today makes us, as hosts, very happy indeed because it was not without some misgiving that this early date for the Congress was decided upon.

Pediatrics has developed so rapidly and the sciences on which it rests have made such great strides that we have much to catch up with since our last meeting in Rome ten years ago. The introduction of the antibiotics, penicillin and streptomycin have changed completely our prognosis of meningeal infection. Even relatively numerous patients with tuberculous meningitis have recovered.

We have made great progress in the treatment of many diseases of serious nature. We have developed techniques costly in time and money to treat a single patient, to save a single life; and yet we have seen during the same period of time thousands of children die of violence, starvation and neglect.

We are gathered together here to learn and evaluate the new, to exchange ideas, to re-establish scientific relationship, and to cement friendships and gather inspiration. All this will make it possible for each of us to return to his home better able to care for children, to cure and prevent their disease. To this our first duty,

the preservation of physical health and cure of disease, we have in the past given our main emphasis, and rightly so.

There is a second duty that we have to which I want to call particular attention; namely, our common responsibility for the welfare and development of all children in all countries of the world.

We pediatricians have, more than any other group, the power to influence the early education of infants and children and direct it into channels that will lead to more co-operative living. The physical and mental health of the individual infant, child and adult is important for a healthy world. Co-operative living consists of the successful application of the Golden Rule to individuals in the family, to the local community, to the nation, and, finally, to the world. As advisors to parents in the earliest education of their children, we have an important role to play in the problem of world peace.

Let us realize that only he is a true pediatrician who thinks of all children as though they were his own.

By **Dr. Edward M. Bernecker**, Commissioner of Hospitals:—

Dr. Helmholtz — Distinguished guests from all parts of the world:

New York City is proud indeed to be host this week to the several thousand eminent specialists in child health gathered here from some sixty different countries to take part in the Fifth International Congress of Pediatrics.

It is my distinguished privilege this morning to extend to each and all of you the City's official welcome on behalf of His Honor, the Mayor, and through him, of the people of the City of New York — and I assure you it is a warm and cordial welcome.

As the first City in the world to appropriate public funds to carry out on an organized basis health care for its children, New York has long had a special interest in the work of pediatricians and has watched with justifiable pride the growth of this service in New York City. Largely through the utilization of the collective skills and zeal of its pediatricians, this City has maintained one of the lowest infant mortality rates in any city in the world. Today

less than 28 of each 1 000 babies born alive die in that first dangerous year of life, but although we pride ourselves that we have reached a degree of eminence, we are not unmindful of the great contributions that have also come from abroad.

I hope that all of you, especially those of you from other cities and other countries, will take time while you are here to visit our children's hospitals and to see how we in this metropolitan community are carrying out wide child welfare and child health programs.

Special arrangements have been made for all visitors to see children's health centers, hospitals and infant health stations. Our pediatricians will, I am sure, welcome your visits and will in turn be eager to avail themselves of the fruits of the experience in other cities and other lands.

It has been said that we live in and for our children and that civilization slowly progresses that way. Therefore, it is significant that the first major international medical conference to be held after World War II should be in the field of child care.

I understand that your last meeting took place some ten years ago and I know that I express the sentiments of His Honor, the Mayor, and the fervent hopes and prayers of all New Yorkers, that this Congress will make significant and world-wide contributions for the better care of children, whose great task will come only too soon in helping build a peaceful world.

By **Thomas Parran**, M. D., Surgeon General, U. S. Public Health Service:—

On behalf of the government of the U. S. A., I have the great honor today not only in having the privilege of greeting you personally but also in being delegated to extend most cordial greetings and to bring you a message of welcome from the President of the United States. This is President Truman's message:

«The United States is honored to be host to the Fifth International Congress of Pediatrics. We welcome particularly the distinguished scientists from other lands who have come here to pool their knowledge with that of American pediatricians so that children everywhere may lead healthier lives. To promote the health of children the world over is a part of our task of building permanent world peace.

«Recognizing the interdependence of nations in the field of health, I have urged prompt adherence of this Nation to the constitution of the World Health Organization, which is dedicated to the principle that 'the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being.' You, the leading pediatricians of the world, can make a great contribution toward this goal. More than any other group you have brought the benefits of preventive medicine to the individual. We owe to you much of our knowledge of how to keep well — which is an even greater blessing than the knowledge of how to get well.

«With my greetings to you go my sincere wishes for the success of your conference. Children are the world's most priceless possession. As guardians of their health, you build our hope for a brighter tomorrow.»

Very sincerely yours,
HARRY S. TRUMAN.

I should like to underscore President Truman's tribute to your leadership in the field of preventive medicine.

You pediatricians know that the promotion of health and treatment of disease are integral parts of a single health problem. Your leadership has been outstanding in demonstrating this fact to the public.

Pediatricians in every land have led the medical profession in the practice of preventive medicine, during a period in which the death rates from childhood diseases have been rapidly reduced in most countries. In the U. S. A., between 1905 and 1945, diphtheria death rates dropped 95 percent; pertussis, 85 percent; measles, 97 percent. Sample studies conducted in 1936 in 28 American cities indicated that 61 percent of the children had been immunized against diphtheria and 85 percent had been vaccinated against smallpox by the time they were eight years old.

Since 1916, the death rate of infants under 1 year has dropped from 100 per thousand births to 38.3 per thousand. In the short span of 12 years, maternal death rates dropped from 6 per 1 000 live births to 2.1. Since the turn of the century, almost thirteen years have been added to the life expectancy of the average American male at birth. But since that time, his life expectancy after 25 years of age has increased by only four years. More than any other age group, children have reaped the benefits of preventive medicine.

An important reason for this result is that pediatricians have developed effective methods of making parents aware of its value. You have established routine immunizations as a part of the thinking of parents. You have advanced the science of child nutrition and you have seen to it that parents use this knowledge. You fought, and to a large degree, you have won «the battle of condensed milk». You have impressed parents with the necessity of having regular, periodic examination for their children. In short, you are making the facts of good child care a part of the *mores* of our people.

Our progress toward better child health in the United States has been very uneven. Many of our children are not provided with the high quality of service we have developed. There are three principal obstacles to our goal of giving all our children an equal opportunity for good health.

First, there is a lack of public health services, health centers, and hospitals in many parts of the country and particularly in our rural regions. One-third of the counties of this nation lack the services of an adequately staffed, full time local health department. Forty million Americans live in these counties, with no trained health officers to plan and coordinate comprehensive public health programs; no public health nurses to assist families with their health problems; no sanitary engineers to assure them of a healthful environment in which to live.

Second, there are not enough physicians, dentists and other health personnel. This is true of all sections, but in some the shortage is particularly acute. The States of New York and California, for example, have three times as many physicians per unit of population as has the State of Mississippi. The same is true of hospital beds.

Third, there is a substantial part of our population who do not receive adequate medical care because the cost of such care is beyond their means.

A national policy has been formulated in the Hospital Survey and Construction Act to overcome, at least in part, the shortage and maldistribution of hospitals and health centers through Federal aid. As yet, however, no comparable programs have been

developed to meet the need for personnel or to assure all income groups of access to adequate health service.

The Public Health Service has been studying this problem for some time and recently has undertaken joint studies with the Council on Medical Education of the American Medical Association. Since present and prospective shortages of well-trained medical and related personnel constitute, in my opinion, a great obstacle to better health, I am hopeful that these studies may lead to corrective action.

Efforts have also been initiated to solve the third barrier to better health — the economic problem. Congress is now considering legislative measures designed to bring the benefits of modern medical knowledge more fully to all of our people. There is general agreement throughout the Nation that this must be done; that it is fundamental to the Nation's health. The principal disagreement is whether the approach to the problem shall be limited to low income groups or shall be more comprehensive. In view of the urgency of the need, I believe that we can and should resolve these differences promptly so that at least a start can be made toward our goal of making available adequate medical care for all the people.

Encouraging evidence that voluntary, professional and official organizations working together can solve these health problems is to be found in a nation-wide survey of child health services sponsored by the American Academy of Pediatrics. There has developed a partnership on a large scale between an organized group of physicians and their government. The study is primarily the responsibility of the Academy, but the Children's Bureau and the U. S. Public Health Service are also participating, contributing staff, space, equipment, technical advisory service and funds.

For the first time a national medical organization has assumed responsibility for collecting data on which they could plan an action program for making essential services of a high quality available to all mothers and children in the Nation.

Remarkable interest has been shown by local communities. What were originally considered secondary objectives of the study, namely, to interest physicians, to arouse state and local groups to

action and to provide data for local planning, have become as important as the primary objective of gathering data for a national report. In fact, the publication of the national report has been delayed because it seemed more urgent to give the data first to the States.

Results of the study are now being tabulated and when the job is complete, we should have the answers to such questions as these:

What proportion of the care rendered children is given by general practitioners?

What special pediatric training have the physicians had who are caring for children?

What proportion of the total visits to children by general practitioners and by pediatricians is for health supervision?

How many children are admitted to hospitals annually?

What kind of hospitals give pediatric and new-born care?

What proportion of school children attend schools which have some sort of school health programs? What is the nature of such programs and who operates them?

The answers to these and other questions contained in the survey will give us the needed facts on which to build a health program that will assure every child in this Nation of the opportunity to enjoy health. Large sums of money from State and local governments, the Federal Government, and private sources are being spent on the study. The total cost will be more than a million dollars. Skilled personnel from both voluntary and official organizations are devoting their time to the project, convinced that the development of an adequate child health program deserves high priority.

The money and the time will be justified only if we make practical use of the knowledge we will have gained. The American Academy of Pediatrics took upon itself a heavy responsibility in making the survey. For that step inevitably obligated them — as I am sure Academy members realize — to take a second and far more difficult step: namely, to use this knowledge to develop a nation-wide program of child health services.

The plan followed in the conduct of the survey may well sug-

gest the approach to the larger task of making good health services available to all. Having seen the need for the survey, forces were mobilized to meet it and government aid was sought for those aspects of the work which would have been impossible or uneconomical to do through nonofficial sources.

The action phase of the program can be achieved in the same manner. Through Academy leadership, coupled with aroused public interest, the aid of Government can be enlisted for those phases of the program which the people are unable to do or cannot do so well or so economically for themselves. This follows our traditional American pattern.

I wish to take this occasion to assure members of the Academy that they can rely upon the continued cooperation of the Public Health Service in this undertaking.

While I have confined my remarks to the activities of American pediatricians, I recognize, as do the members of this Congress, that the health of children in war devastated areas is a matter of greatest urgency. The problem there, as in this country, is not solely a medical one. As long as children have insufficient food and live in unwholesome environments, we cannot hope to reap the full value of pediatric knowledge. Preventive care of children is a social and economic, as well as a medical problem.

Fortunately, a solution to the problems of child health is now within the realm of possibility. In due course, we can, if we will, achieve on a world scale the high degree of health which is defined in the Constitution of the World Health Organization as: «a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.»

International meeting such as this are helping to bring us closer to this world health goal. I know I speak not only for myself but for the people whose government I have the honor to represent when I extend to you best wishes for a fruitful and productive conference.

By **Katharine F. Lenroot**, Chief, Children's Bureau, Social Security Administration, Federal Security Agency, Washington, D. C.:—

It is indeed a privilege to add my welcome on behalf of the United States Children's Bureau and my associates in the Bureau

who are your colleagues in the great profession of pediatrics. I regret particularly that my associate, Dr. Martha M. Eliot, is not able to participate in this conference. She has been lent for a brief period to the International Children's Emergency Fund as its chief technical consultant, and is now in Europe in connection with the Fund's work.

It is a matter of great significance that this gathering is being held here in the city which is to be the headquarters of the United Nations. The presence of men and women from all over the world whose lives are dedicated to serving children is a reminder to the governments and peoples of all Nations that a common concern in the health of children can be, if we wish to make it so, a powerful catalytic agent for the kind of peace that binds the hearts of men in a great endeavor. When people meet around the problems and needs of children they talk a common language. When people take pride in their achievements for children their pride can be shared by everyone. When people are willing to test political and economic programs by their effects on the lives of children they have a common yardstick of values. The work of the United States Children's Bureau has been built around the concept that child welfare is a test of the success of democratic institutions.

The profession of pediatrics and the work of the Children's Bureau are based upon the whole child as the focal point of our endeavor. Concern with the functioning of one particular organ, the prevention or treatment of a single disease, or one aspect of the life of a child must be subordinate to our understanding of the physical and mental health of the whole child as he functions in relation to his environment. Pediatricians in many lands have been the first to recognize the need for such a comprehensive approach to the problems of childhood and to take leadership in developing private institutions and departments of government basing their programs upon such an approach. I am thinking particularly of a great pediatrician and pioneer in child health work in one of the most advanced republics of the western hemisphere tested by what it does for children, the late Dr. Luis Morquio, founder of the child welfare work of his own country, Uruguay, and of the first inter-governmental organization to be

devoted solely to the interests of children — the American International Institute for the Protection of Childhood — one of whose officials is a member of this Congress.

The Children's Bureau is a small bureau as government agencies in Washington go, but one with a large mandate from the Congress of the United States. We are instructed »to investigate and report upon all matters pertaining to the welfare of children and child life among all classes of our people.« In addition the Children's Bureau administers, under authority delegated by the Federal Security Administrator, grants of money to the States, appropriated each year by Congress to help support the child health and child welfare services provided by our State and local governments. At present these grants total \$22 million a year for maternal and child health services, services for crippled children, and social services for children, particularly in rural areas. The Children's Bureau is part of the Social Security Administration of the Federal Security Agency — an agency which has other important programs affecting the health, social welfare and education of children, including among other functions Old-Age and Survivors Insurance and administration of grants to States for aid to dependent children in their own homes.

The Children's Bureau throughout the 35 years of its history has been deeply interested in international programs for children, and our organization now includes a branch devoted to international cooperation. Our own work has been greatly enriched by contact with visitors from abroad as well as by visits to other countries, when practicable, by members of the staff. We hope that it will be possible for many of you to come to see us while in the United States and we shall be glad to make available any information of help that is within our power to give.

You will find in the United States examples of very skilled and adequate service for children as well as places where there is little opportunity for bringing to the needs of children the resources made possible by modern science. Progress in recent years, through the cooperation of the Federal government, the States and local governments, the professions and citizens' organizations,

has been great. Your President, Dr. Helmholtz, has been one of our most helpful and valued colleagues.

Since 1934 the maternal death rate, formerly one of the highest in the world, has been cut about two-thirds, and the infant death rate more than one-third. If all our States did as well as the States with the best records in saving babies we would lose about 31 000 fewer babies in infancy than now succumb. It is estimated that we could save the lives of many thousands of premature babies each year if adequate service for the premature were available in every community. The infant death rate in some States is three or four times as high as in the States which have done the most in saving infant life.

A great deal has been done for certain types of handicapped children, notably children suffering from poliomyelitis, but well-organized programs for the care of the 500 000 children in the United States suffering from rheumatic heart disease and the 175 000 suffering from cerebral palsy are available only in a small proportion of the communities of this country. We have hardly begun to provide adequate service for the health of children of school age. Mental health programs, which have such an important contribution to make to the total health of the child, are in their infancy. We need to extend greatly our services in rural areas.

I cite these figures to you to indicate some of our unfinished business in the field of child health. Like most countries we are still woefully deficient in professional personnel and facilities for providing care. While in some States as many as 98 out of 100 births take place in hospitals, in others the rate is 31 out of 100.

You gather, as you should, from such figures as these that we have much to do within our own country before we can say that all our children have a fair start and an even chance in life. In fact, we have far to go to measure up to what some of you have already achieved. The picture here, however, is not all dark. You will find, as you travel over our country, some excellent work being done which will be an inspiration to you as it is to many of us. Dr. C. Anderson Aldrich is directing one of the most significant research projects in Rochester, Minnesota, providing complete health supervision for all children born in the city, throughout in-

fancy and the preschool period. Our State health departments and State crippled children's agencies are pioneering in important ways in developing new health services and types of medical care for children. Many of these projects receive help from the Federal Government through the grants administered by the Children's Bureau.

Dr. Parran has told you of the great research project undertaken by the American Academy of Pediatrics, in cooperation with the United States Public Health Service and the Children's Bureau. No other group of physicians has been so far-sighted and so public spirited in volunteering to measure the health and medical-care needs of the people they serve, and to assume responsibility for helping to meet those needs. Already the American Academy has established a Committee for the Improvement of Child Health and directed this Committee to draw up suggestions on how the pediatricians of this country can work with communities in building better health for children.

There is great wisdom and social vision in this attitude of our American pediatricians. Like the peoples of many other nations, our people are showing great interest in finding some way to make medical care and health services available to all children and to spread their cost more equitably. Committees of Congress have given careful consideration to a number of proposals for making health services, including child health, more generally available. As you know the United States does not have health insurance as part of its social security program. We are learning in this country that the health and welfare of children in all parts of the country must be assured if children in any part of the country are to be safe. The same is true for the children of the world. As one way of meeting some of the most urgent needs of children in war-devastated countries the International Children's Emergency Fund was established by a Resolution of the General Assembly of the United Nations adopted last December. The Congress of the United States has already authorized contributions to the Fund, and other countries have indicated their willingness to assist. Voluntary contributions are greatly needed — a world-wide campaign is being planned by the United Nations under the »United

Nations Appeal for Children». The resources of the Fund will be used in the first instance to supplement the essential food- and other supplies needed to alleviate malnutrition and disease of children and to safeguard the health of expectant and nursing mothers. It is very encouraging to know that the World Health Organization and the Food and Agriculture Organization of the United Nations have set up a joint technical committee to advise on the child feeding program. Some of the members of this Congress have been appointed members of this Committee.

My associate, Dr. Martha M. Eliot, has spelled out to some of you the role that all of you can play in making this a dynamic and effective aid for the children of stricken countries. May I repeat her words:

»You, who make up this great body of the world's physicians, whose primary concern is the health and welfare of children, can influence in a large way the success of this international effort for children. You can influence the standards of care established by the Fund by discussing them with your national representatives on the Executive Board of the Fund, and by helping to shape the program of health and welfare service in the recipient countries. You can assist materially by arousing the Governments and the peoples of your countries to contribute to the Fund in the form of money, food, clothing, medical supplies and equipment, and in offering opportunities for training professional workers in all fields. You know the needs of children in your countries as well as any other group of world citizens.»

Tenderness and compassion for childhood suffering are the best reasons for organized help to the children of war-torn lands, and later if possible of countries where mass suffering and poverty prevail. Yet the need for international cooperation in behalf of children has wider implications. In this postwar but gravely unsettled period, we have set our faces toward the building of a world order where freedom and democracy can live and grow.

The only way in which we can achieve a peaceful and ordered world is through people. The most perfect political system is

valueless unless the people using it are animated by right ideals and have the strength of body and character, the intelligence and the social effectiveness necessary to make it work. Our major concern, therefore, must be the children and youth who, tomorrow, will be at the helms of national governments and of national and international organizations and institutions. In service to them, you who are members of this first post-war International Congress of Pediatrics, can give inspiration, encouragement, leadership, and practical help.

By **Frederick Osborn**:—

The opening of a great Congress of Pediatrics at this time is of special significance. It is an act of faith. Faith that all of the countries represented here — and they constitute indeed the great majority of the countries of the world — believe that a better world is possible for ourselves and particularly for our children.

Certain men who are rulers of a large area, and of some ten per cent or more of the people of the world, have declared that the particular economic system to which they aspire is the only acceptable system. They assert that their system is not compatible with any other means by which men provide food and security for their families. In spite of the stand they take in international conferences in their advocacy of world peace and disarmament, they simultaneously state publicly to their people and to all the world that there is an inevitable conflict between their system and all other systems, and that in preparation for this conflict they must be heavily armed, no matter what it costs them in hunger and privation; that they must extend the territories which they control in order to be better prepared for this conflict, and that in the final climax one or the other system will be destroyed.

This is fanaticism. There is no such rigid line between one way of men's earning their living and another. Each merges into the other. The ultimate trial of what is best will be not what people say, but what actually best provides for the wellbeing of the mass of the people, whether it be found in Socialism or Communism or individual effort safeguarded by the restraints of the law, or, as is more likely, by some combination of all three.

To say that conflict is inevitable for economic reasons is as dangerous and as wrong as it was to say three hundred years ago that Catholics and Protestants of the same Christian faith could not live together in the same country without cutting each others' throats. We have learned better than that. There are no longer great religious wars, nor does anyone propose them. Each man practices in peace the religion he desires. Some day we will learn the same lesson in the economic field, and the economic dogma of the past will not be marshalled as an argument for inevitable wars in the future.

Meantime, we are passing through critical times. In these times we can do no greater service than to prove by our own acts that there are men and women, and many of them, who seek to do good for future generations with no thought for themselves. They are the prophets of generations yet unborn. As such, I greet you today. I give you the fellowship of all those who are striving for the success and permanence of the United Nations. I wish you success in your efforts, that the children of the world for generations to come will know a better life because of what you here have been able to do for them.

Plenary Session—Nutrition.

RELATOR.

Observations on Nutrition, Health and Physical Development in the British Zone of Germany 1946—47.

By **R. A. McCance**, M. D.

Medical Research Council Unit, Wuppertal, B. A. O. R. and Cambridge, England.

The spectacle of a great nation, prostrate and short of food, excites feelings which vary with the nationality, nature and upbringing of the observer. Some can regard it with supreme indifference. I am not one of these, but I have never had the provocations and humiliations of an occupation to sharpen my feelings of callousness and revenge. Some are moved with pity and can think only in terms of relief. With these, I can sympathise, but feelings of this kind may become obsessions, and they are apt to sway people to do things which they would never have done had they been in possession of, and able to analyse, all the facts. A few with the outlook and specialised training, which most of us here have had, can see in it a chance of doing mankind some good by improving his knowledge of physiology and disease, and it was mainly with these feelings in our minds that Dr. Widdowson and I set out in March 1946 for a tour of the British Zone. We found enough undernutrition to convince us that an expedition would be justifiable, and, with the aid of the Medical Research Council, we established ourselves in Wuppertal where we had the facilities of three small wards in the Städtisches Krankenhaus, Barmen, and one floor in the beautiful I. G.-Farben Laboratories in Elberfeld. There we have been for the past 15 months. The main object of our work was to study the effects of malnutrition upon

the physiology of the individual. Before I describe any of this work I must give you a short account of the German rationing system and its consequences, for without that it is impossible to understand the situation.

When we started work in June 1946 the ration for the normal consumer was just over 1 000 Calories a day, and had been so for three months. Over half of these Calories were derived from bread, and there were no potatoes in the ration. (The details will be given in a table). The country was still in a state of considerable disorganization. Few German cars were on the roads, and there were scarcely any passenger trains. Most people in the large towns probably had little more than their bare rations, and there was a considerable amount of undernutrition among the general population of these towns, and in the prisons and other places where the rations formed the only source of food. (A table will show the fluctuations in the official rations during 1946 and the supplements allowed for children). The trouble about the official rations in the latter half of 1946 was that they were never all obtainable. Nahrungsmittel, for example, which consisted of things like macaroni, oatmeal and semolina were rarely if ever available, and nothing was issued instead. The increase in the total ration to 1 550 Calories a day in October coincided with the dock strike in the United States, and the bread supplies broke down several times. In Wuppertal, for instance, there was virtually no bread in the shops for at least a week, and distribution failed again for short periods in November, January and February. There has been little improvement in the situation in 1947, and the official rations have never all been available. Only about half of them could be obtained in May of this year.

Children and pregnant and nursing mothers have always had special supplementary rations. (Their Calorie values and other details about them in June 1946 will be shown in a table). Women who were nursing their babies received the child's ration as well as their own, so that theoretically they had an ample sufficiency of calories and a generous ration of milk. Milk became very scarce during the winter, however, and everybody's ration was halved. Since the beginning of this year children of 6 years and

over have had no full milk at all. Their ration was 1/8 litre of skimmed milk a day and sometimes none was available. It will be quite clear to any one who is familiar with children's appetites and requirements that, although the rations increased as children grew older, they did not increase nearly enough. Children in the 2 youngest age groups may have been reasonably well off, but those aged 10 to 18 were deplorably short of Calories, and they certainly needed more milk. Even after all the increases that took place in the official rations in the latter half of 1946, this group got no more than 2 000 Calories a day. School children were generally provided with soup in the middle of the morning in addition to their ordinary rations and this may be reckoned to provide a further 300 Calories a day.

Against this rather gloomy picture must be set the fact that during the past year the population has undoubtedly improved in its nutritional status. There are many reasons for this, but it is difficult to define all of them. In the first place there were many official reasons for obtaining supplementary rations; so many indeed, that we have often wondered how many normal consumers there really were in Germany. Secondly there has been an extensive increase in the cultivation of individual gardens. A third reason has certainly been the development of what the Germans call 'Hamstern'. The term hamstern is derived from the name of an animal which stores food for the winter. People set off from the towns, their rucksacks full of whatever barter goods they can command, and they tour the countryside in search of farmers who are willing to exchange food for some of their wares. At first this started in quite a small way. People visited the farms near at hand, and traded their own possessions, sheets, toys and clothes, but later the trade became more organized and the farmers more particular. Factories were expected to and did supply their workmen with barter ware, and as the train services improved people began to travel all over the British and, later, the American Zones on these expeditions. Women went as well as men, and all endured considerable privations and hardships in this struggle for extra food. A variant of this system was the barter of services for food. A builder from a town would offer

to build a barn for a farmer in exchange for his food. People began to look up old friends in the country and pay them long visits, often taking their children with them as well. They would work on the farm while they were there in exchange for their food and board. The economic hopelessness of this way of getting food will be appreciated by any one who gives it a moment's thought. Homes are constantly broken up, and factories must reckon to have many of their employees away at any one time on Hamster-tours. The employers are quite powerless, for when a hungry man can earn in 3 or 4 days enough money to buy his official rations, he naturally feels that the remainder of his time is much better spent hamstering or gardening than plying his proper trade.

Most of our work in Wuppertal has been concerned with adults, particularly men. We are, however, making one or two investigations on children, and I should like to tell you a little about those now.

We began with the babies at birth. Were they smaller than they should have been, or than they were in times of plenty? Three large maternity hospitals are co-operating with us in this, two in Hamburg and one in Wuppertal. Records have been kept of all births during the past year, and the data are being compared with data for 1937 which is readily available in the hospital records. Only a small amount of our data has so far been analysed, but a chart will be shown giving a preliminary analysis of some of our Wuppertal figures. This diagram was based upon the birth weights of 718 babies in 1937 and 1 536 babies in 1946. We shall ultimately have 4 or 5 times these numbers. You will see that the babies undoubtedly tended to be heavier in 1937 than in 1946, and this was true also when the boys and girls were considered separately, and when primiparae were divided from multiparae. If the full numbers confirm these preliminary findings, as I expect they will, we shall have the interesting task of finding out whether the babies were shorter as well as lighter in 1946, and whether the gestation periods were as long. We have data about the amounts of milk the mothers produced each day they were in hospital, so we are hoping to find out something about the effect of the present dietary regime upon the ability of the mothers to

lactate. We are also trying to follow this up with a study of the length of time the mothers are able to feed their babies after they leave the hospital.

We have never made any large scale nutrition surveys of the child population, but in connection with a feeding experiment which we are doing at one orphanage at Duisburg we have made a very detailed clinical examination of about 150 children there. We have no proof that they are truly representative of the general child population, but we have reason to believe that they are no worse, and probably better cared for than their fellows. They have for our purposes the great advantage of having had little but the official rations for children, so we can get some idea of the effects of these known rations on heights, weights and physical fitness.

The children start the day with 2 or 3 slices of bread, spread with the merest trace of jam, and they have black »Ersatz« coffee to drink. At 10 a. m. they have $3/4$ litre of »Schulspeise«, that is soup consisting chiefly of American army biscuits ground to a powder, mixed with water, and flavoured with a small amount of chocolate. At 12 noon they have their midday meal which consists of more soup, made from potatoes and other vegetables, and they eat anything up to 142 litres of this. Then at 4 p. m. comes more soup which is usually made from semolina and water, with a little sugar, and it contains the skimmed milk ration for the day. At 6 p. m. the children have 2 or 3 slices of bread with a 'scrape' of jam or with a little cheese, but they have nothing to drink at this time and at 6.30 they retire to bed. The weekly meat ration is all eaten on Sundays.

Tables will be shown giving the heights and weights of the orphans living on this diet compared with the figures given by O'Brien, Giralick and Hunt for American children of the same ages. The German children are shorter and lighter than American children, and their $\frac{\text{weight}}{\text{height}}$ ratio is also lower. This was only to be expected, but there are two features of considerable interest about these figures. The first is that the heights and weights of the German children deviate further and further from the Ameri-

can figures as the children get older, presumably because the rations for the older children are less adequate. The second is that the boys are always worse than the girls. Boys of 13 and 14 are well known to have colossal appetites, and to eat far more than girls of the same age, but it will perhaps be surprising to many of you that they require more food at the younger ages, and go to the wall if they do not get it. It was not, however, a surprise to us, for in her study of the freely chosen food intakes of 1 000 individual children of all ages, which she made in Britain in 1936—1939, Dr. Widdowson found that the freely chosen intakes of boys tended to be greater than those of girls right back to the age of 3 or 4. The clinical examination of the German children at the orphanage has confirmed the evidence of their heights and weights. The boys have poorer posture, their muscular development is not so good, and their skins are not so healthy, but there are no signs of vitamin deficiencies in either sex.

I do not wish to leave you with the impression that the children of Germany are impoverished, half-starved little miseries, silent, lackadaisical, and incapable of enjoying life. Just the reverse. The children at the orphanage never seem to be ill. They always have colds, of course, but there hasn't been a child in the sick room for months, and their life seems to be one of perpetual motion. I have had plenty of chances of observing German children at play in the last year, for I walk through a section of tenement slums several times a day between our laboratory and our house. The streets are a screaming throng of children all day long, playing football, whipping tops, roller skating, tobogganing, fighting, climbing up the lampposts, doing in fact all the things that children of that class — and every class — will always do if they get the chance.

I am sorry to think of any child not getting enough food, but I am not on the whole very worried about the nutritional health of the children in Germany. When plenty returns, as I hope it soon will, I look forward to watching these children taking full advantage of it and making up for some at any rate of the chances they have missed.

May I say two things in conclusion. Firstly I want to thank the organizers of this conference for the honour they have done me in inviting me to come here and to speak. Secondly, I wish to say that I am only one member of the Medical Research Council unit in Wuppertal. The data I have been placing before you has largely been the work of Dr. Widdowson, Dr. Dean, Miss Thrussell and others with whom I have had the privilege of working. The credit, if any, for these results is theirs, not mine.

RELATOR.

The Nutritional Status of Rotterdam Children During and After the War.

By **J. H. P. Jonxis**, M. D., Rotterdam, Netherlands.

Hunger has always been the companion of war. This time Holland was one of the countries which suffered most. So we were placed in the middle of an involuntary mass-experiment. The conditions in which this experiment occurred caused it to be one of nearly pure starvation. In most countries afflicted by famine, infectious diseases spread rapidly and disturb the picture, but in Holland it was possible to have infectious diseases more or less in hand during the whole starvation-period. Thus we could study starvation in a more or less pure form and we have tried to take advantage of the opportunity afforded by this dramatic experiment.

Especially before the liberation, conditions for scientific work were so difficult that the collected figures are not at all complete. After the liberation we could follow the improvement of the nutritional status of the children. This is of special interest because scarcity of food will remain for some time in Europe and we shall have to be as economical as possible with our food. On the other hand we shall have to try to make our children as healthy as possible, that is in many respects better than before the war. This can only be done by tracing the defects in our present rationing and by administering in one way or other the lacking nutrients to our children.

Real hunger existed in Western Holland from October 1944 to May 1945, that is for about 7 months. It followed a period during which rations had already been on the lower side. It is not possible to calculate exactly what amount of food the children really got during the hunger period, but we can be sure that in the larger towns most of the children between 4 and 10 years did not get more than 800 calories daily. The protein-amount was less than 20 g and contained only 5 g of animal protein. The amount of fat was very low. So were also the amounts of minerals, vitamin A and vitamin D. The uptake of the vitamins of the B group and vitamin C was mostly a little bit better.

At first the children did not gain weight and later even lost it. Their growth in length ceased, their total behaviour remained rather normal for some time, but at last the children became irritable and lost interest. Gastro-intestinal disturbances were very common, especially when the children got greater amounts of sugar-beets, the common food at that moment. The hemoglobin was normal or slightly diminished. Oedema was rare. Blood-protein levels were somewhat lower on the whole, but I have seen cases of oedema with nearly normal protein-levels in their serum. All other levels in the blood had a tendency to be low. Systolic and diastolic blood pressure were low. After the end of the war the blood pressure went up. I have the feeling that for a certain group of children the average blood-pressure is a good indicator to follow their improvement. Signs of deficiency diseases were seldom seen on the whole. I have the feeling that this was caused by the low metabolism. Scurvy was rare. Younger children under 3 years in Rotterdam even during the starvation period got 300 000 units of vitamin D two times a year. So rickets was and is very uncommon. But older children complained of pain in the bones of their legs during the last months of starvation and showed low calcium and phosphate levels in their blood. These painful legs could be promptly cured by administering greater amounts of vitamin D. It is not clear to me whether these painful bones, which were slightly demineralized, were only the result of a lack of calcium or whether there was at the same time a lack of vitamin D. It is possible that this vitamin could not

be made normally in the skin. Because these children did not grow, they needed less calcium than normally. On the other hand the low calcium-intake and the high amounts of phytic acids and oxalic acids in their food will have made their calcium-balance negative. Extra vitamin D will have helped to restore the equilibrium.

The problem of vitamin A is rather complicated. The children between 4 and 10 years got scarcely any vitamin A at all, but from vegetables they got some thousands of units of carotene daily. In the blood we found the A values mostly very low. Carotene values were on the lower side of normal. I did not see, although I inspected many thousands of children, one case of keratomalacia. On the other hand I saw many cases with hyperkeratosis and many children with defects of the epithelium of the skin, especially when there had been a scarification. The X-ray pictures showed augmented shadows around the bronchi, especially in the lower lung fields. To a number of children I gave 17 000 units of vitamin A daily for a fortnight. The effect was striking. The skin became normal and in some cases the children even gained some weight with a diet as before. The X-ray picture became more normal. The blood-values of A went up.

At the same time I gave another group of children the corresponding amount of carotene. In these cases there was no improvement. In the blood the carotene level rose to high values, an indication that at least a part of the carotene had been absorbed, but the vitamin A level improved only slightly.

This experiment shows that in these children carotene cannot be split into vitamin A. When we did not give pure carotene dissolved in rape-oil, but when we gave the children a corresponding amount of red palm-oil with the same carotene content, we found results which were only slightly less than those of the vitamin A administration. At the same time it could be demonstrated that during starvation adults can split carotene into vitamin A just as under normal conditions. It seems that children need an additional factor for the conversion of carotene into vitamin A, which factor is present in red palm-oil.

After the liberation, when the children had not yet got enough

vitamin A to supply their deficiency, I repeated these experiments. They gave the same results, but it was clear that somewhere in the food of the children, perhaps in the chocolate, the same additional factor was present as in red palm-oil.

Even under more normal conditions the conversion of carotene into vitamin A remains a rather uncertain process in children. In our surveys in Rotterdam in recent years we have found that A values of the blood remain low as long as the A content of the food is unsatisfactory. The children get enough carotene, and their carotene-values are normal. Addition of vitamin A to the diet not only raises the blood-levels but at the same time improves the condition of the skin and shortens the dark-adaption-time. Because there is a lack of vitamin A in the world, it would be of great importance if we knew more about the factors which improve the conversion of carotene into vitamin A.

I did not see signs of deficiency which could be caused by lack of some factor of the vitamin B-complex. Adding B-complex to the food, especially B₁, gives no improvements.

In comparison to older people children can better stand starvation. Of 50 000 children between 1 and 5 years in Rotterdam 300 died (in contrast with a normal expectancy of 60) during the first 4 months of 1945. Many of these deaths were caused by infectious diseases. It seems that children can better adapt themselves than older people can. This adaptation of the younger may have been the factor which made possible the survival of the human race in prehistoric times.

After the liberation, as soon as food became available in abundance, the condition of the children improved. Only a few of them who were in a very bad condition, some with oedema, all with intestinal disturbances, died. Autopsy showed in some of these cases a fatty liver with a beginning of cirrhosis, perhaps caused by a lack of choline or methionine. We treated our worst cases with a diet rich in protein and vitamins. When there was dehydration, plasma-infusions were given. Feeding by mouth of protein hydrolysates had no effect.

When the war was over we could follow the improvement of

the condition of the children and we could make plans how to bring back their nutritional status to a normal one.

The diet which the children get during the years since the war remains with some seasonal changes about the same. For children between 4 and 9 years the diet consists of about 2 000 calories with 60 g of protein, of which nearly the half is of animal source, and 50 g of fat. The iron-content of the food is on the lower side, the vitamin A content is low, the amount of carotene is normal. The food contains practically no vitamin D. The vitamin C content changes with the season between 30 mg and 60 mg. In many cases the children get more. Other nutrients are available sufficiently.

At first the children improved rapidly. When we made a survey in the autumn of 1946 the results were again better than in the spring of that year. Since then there are no further improvements. We have not enough exact data to compare the situation now with that of the children of a same class and age before the war. But such a comparison would not be of great value because the children of the large towns in that time of wholesale unemployment were certainly not in optimal condition.

We had the opportunity to compare our children in Rotterdam with a group of Rotterdam children of the same class who had been in Sweden during 8 months. These children on coming back were in a far better condition. Their protein and vitamin A values of the blood were significantly higher. Their skin showed no signs of hyperkeratosis as the Rotterdam children still have. Their hemoglobin was higher. We also compared our children with a group of English children in New Castle. Although we had no comparable blood values it was clear that also these English children were in a better nutritional condition.

We tried to find out why, on a diet which on paper ought to be enough, our children were so far behind the English children and the children from Sweden. When we compared children from slightly different social classes we found that there were only slight differences in the amount of food which the house-wives bought. But there was a great difference in the ways in which

the women used it. The lower the social class is, the greater the losses. That these losses in food by bad handling are really of greater influence on the nutritional status of the children became clear when we made a comparison with a group of children of a children's home where for months they lived on a diet such as I have described before, to which had been added merely some iron and codliver-oil. These children were in far better condition, which can be explained only partly by the additional administration of iron and codliver-oil, but is the result of the better way in which it is used.

We tried to improve the status of the children who live in their normal homes. Therefore we made the following experiment. First we gave different groups of children from 4 to 8 years of age a supplement of iron, vitamin A, vitamin D and milk-protein daily for 6 weeks respectively. The iron administration produced in nearly all cases a rise of the Hb. level. When the hemoglobin did not improve more by giving iron, the children got an additional supplement of milkprotein. This caused not only a greater gain in length and weight than that of a control group but also a further rise of the hemoglobin level.

That addition of vitamin A to the food gave an improvement I have already stated. It is generally accepted that older children do not need vitamin D, but when we added D to the food of a group of children the serum phosphate content showed a significant rise, the calcium level remaining normal at the same time. I believe that this is an indication that these children are not making enough vitamin D on their own and that we can better add some vitamin D to their food.

For these reasons we have decided to give 2 000 units of vitamin A, 800 units of vitamin D and 10 mg of iron to the school-children. To be sure that they really will get it, it will be given at school.

The most important problem, because it has great economical consequences, is the determination of the amount of protein, especially animal protein, which our children need. Our experiments with adding protein to the food of schoolchildren showed that children of all social classes which we investigated improved

by being given more protein. We made the decision that we shall have to give 300 cc of skimmed milk at school daily as additional protein.

To find out if this additional protein has still a good effect when the children indeed get 3.2 g of protein per kg bodyweight daily, the amount which a child of 20 kg gets from his legal ration, we raised for one group in our children's home the protein amount to 5.2 g daily whilst another group got the same increased number of calories in the form of sugar. After 6 weeks the protein group had gained more length and its hemoglobin was 5 % higher than a control-group. It could be expected that the adding of sugar would spare protein and would improve in this way the condition of the children. I did not find in repeated experiments any trace of such a sparing effect. On the contrary, in all my experiments sugar had no or a slightly negative influence.

Perhaps this great need of protein is still the aftereffect of the restriction which the children had suffered previously.

CO-RELATOR.

The Infants and Children of South Africa.

By **Joseph and Theodore Gillman.**

Medical School, University of the Witwatersrand, Johannesburg.

Before making my small contribution to this stimulating symposium, I would like to take this opportunity of expressing my gratitude to the members of the organising committee of this conference for the splendid arrangements they have made in permitting pediatricians and other scientists to foregather to discuss such a vital subject as the welfare of children in health and disease. I appreciate very much indeed the sacrifice and personal effort made by these several individuals who have actively promoted this kind of international collaboration in matters which affect the welfare of the human race. It is a practical step in the realisation of the objectives of the World Health Organization to which 61 nations gave their pledge on July 22nd 1946.

This new health organization, whatever its present limitations, carries a message of hope to many people in different parts of the world. At least those countries who have undertaken to support this international organization will remain indicted as long as their people are denied elementary human rights in the form of security and health. This applies particularly to countries inhabited by mixed populations. It is my object this afternoon, to examine the tasks facing South Africa in fulfilment of her obligations towards her infants and children in terms of the new Health Charter.

Social and Economic Status of the People in South Africa.

One of the introductory paragraphs to this Constitution states:

«Governments have a responsibility for the health of the peoples which can be fulfilled only by the provision of adequate health and social measures.»

South Africa, approximately one seventh the size of the United States and stretching from the Zambesi river in the north to Cape Point in the South, from the Indian Ocean on the east to the Atlantic Ocean on the West is the scene of a great struggle between an emergent black people of approximately seven millions and the dominant European culture sponsored by 2¼ millions white people. In addition, a quarter of a million Indians and three-quarters of a million coloureds or mulattos are clamouring for economic and political emancipation. The outcome of this struggle will undoubtedly influence the destiny of the black population of the entire African continent, estimated at between 120 and 150 millions.

When the first Dutch settlers came into contact with South African tribes in the last quarter of the 18th century, they found a virile people herding their cattle, cultivating the soil and hunting wild game. To retain their land and independence, the tribesmen fought the white man for over a hundred years. The African negroes, conquered and subjected became subservient to a white economy. From that time onwards, the social and economic life of the black people gradually deteriorated; today, their form of

society is rapidly becoming disorganised. Vast numbers are now constrained to depend for their livelihood on the industrial and agricultural enterprise of the white settlers.

While approximately $2\frac{3}{4}$ million Africans are segregated in the specially protected areas of Native Reserves, $2\frac{1}{4}$ millions are found as squatters or labourers on the farms and about 900 000 are congregated in or around urban areas; about 600 000 provide labour for the mines and other industries.

In 1937, statistics revealed that 78 % of the native labourers earned less than £60 per capita per annum, while 55 % received between £9 and £36 per annum, or between 3/6 and 14/- per week. Moreover, about 12 % of the white population have ceased to share in the economic life of the nation and are classified as poor whites (John Burger, 1944).

According to the 1936 census (Official Year Book of the Union, 1941) there are approximately 4 million children below the age of 14 years, consisting of $2\frac{3}{4}$ million natives, 620 000 whites, 100 000 Asiatics and 320 000 coloured. More than half of these children are of school-going ages. Despite the fact that native children of school-going age number well over $1\frac{1}{2}$ millions, only 600 000 were attending schools as compared with 450 000 white children. Health and educational facilities are distributed differentially among the population according to the social status of its component groups. As far as hospitalisation is concerned, although the white population is only one third the size of the African population, there are four times as many beds available for Europeans as there are for Africans. Moreover, the expenditure per bed per day for Europeans in Johannesburg is £1.10.2. whereas for Africans, it is 12/8. Thus, not only are there fewer beds available for Africans, but the cost of the service is less and consequently, as we know in this hard world, the service is correspondingly less efficient. In Johannesburg, there are 180 maternity beds, provided by the Transvaal Province for European women; but among an equally sized African population, without the material assistance of an American mission which has provided 60 beds, now partially subsidised by the Transvaal Province, there would not have been a single maternity bed to accommodate

a woman even in the most complicated labour. This serious omission is now receiving some attention.

As far as the children are concerned, until recently, 170 beds were available for European children in Johannesburg, and only 32 for the African and more needy section of the population. At the new hospital recently erected, another 60 beds have now been provided for the black people. At present, therefore, the more needy black people with four times the number of children, have at their disposal half the number of beds available to the European children.

In education, an even greater disparity exists in the facilities provided for European and African sections of the population. Firstly, education is compulsory for the European until the age of 15 years, secondly, child labour is forbidden, and thirdly, approximately £25 per annum is expended for the education of each European child. By contrast, the education for the non-European is not compulsory, the schools are attended chiefly by girls because the boys, even at a very young age, especially in the rural areas, are constrained by necessity to labour in the fields or to tend cattle, and the per capita expenditure is £2.15.0. per annum, or approximately one-tenth that of the European child. Moreover, in the rural areas in particular, the schools are so sparsely distributed that only a limited number of children can take advantage of the educational facilities. Many of those children who go to school cover the distance on foot, which necessitates their rising very early in the morning. They have a scanty meal and are obliged to continue for the rest of the day without food until they return home in the evening. One of my colleagues, Dr. Keen (1946) discovered that the gain of weight noted in African school children during vacation in the area surveyed, was due to the fact that the children did not expend the great effort in walking the long distances to school and that their meals, although still precarious, were more frequent.

In this connection, the observations of a school inspector in the Transkei — one of the large native reserves — might be quoted. From a survey of 11 000 native school children, he made the astonishing announcements that 84 % had only one meal a

day — 14.9 % had two meals and 0.6 % had three meals. All consumed maize in one form or another — 39 % had access to some milk in season — 8.5 % had green vegetables and 8.0 % had pumpkins. It is not entirely unexpected to find that severe malnutrition is devastating this section of the population.

The discriminative educational measures in South Africa allow the overwhelming majority of children to achieve only a low standard of education — those who leave school are unable to enter the skilled trades and the outlets for the more capable members are highly restricted. Their earning capacity is extremely low and consequently, they live in poverty and squalor. The Africans remain economically the most impoverished and most backward members of the population. While these discriminative measures affect the African as far as his social and economic life are concerned, they certainly do not apply when it comes to the purchase of essential commodities. The price of bread, milk, butter, meat, in South Africa is the same for everybody, irrespective of race, colour or creed.

Economically and educationally, it is clear that in general, the Africans are 5—10 times worse off than the Europeans. The South African Government therefore, has not accepted the responsibility for the health of her people without prejudice, and has only made adequate provision through health and social measures for a limited section of the population. The new generation of Africans are illiterate, underfed, wretched human beings, products of the slums of town and country. In surveying the state of health in this country, it is not entirely unexpected that the members of the National Health Services Commission (1944) were led to make the following remarks in connection with the unsatisfactory health of the Africans and other sections of the community.

«One factor stands out pre-eminently — the grinding poverty of almost all the non-European population of this country. The total national income accruing to the whole population of ten millions is about £400 000 000 per annum or £40 per head. This average does not, however, give a true idea of the position, because the income is distributed very unequally. A small section of the community lives on a high standard while the vast majority live in great poverty. This is in fact one of

the poor countries of the world, its poverty being partly the result of the country's geographic and climatic conditions and partly the result of the economic structure which it has created.»

The infants in South Africa.

Again we may revert to the Constitution of the new Health Organization.

«Healthy development of the child is of basic importance. The ability to live in a changing environment is essential to such development.»

In this highly economic and practical world of ours, survival and health are functions of wealth. In all economically and socially advanced countries, one of the most sensitive indicators of national welfare is the infantile mortality rate. In South Africa the mortality rate for the European section fluctuates between 30 and 53 per 1 000 with an average of 43 per 1 000 live births for the whole country. This figure is not entirely satisfactory, but compares favourably with the infantile mortality rate in other parts of the world. It is this figure which is officially quoted as reflecting the state of well being of the infants in South Africa. An entirely different picture emerges when the mortality rate amongst the non-European children is taken into account. In one of the native territories, Dr. Mary McGregor (1944) discovered that only 500 out of every 1 000 live babies born, reached the age of 18 years. Moreover, 300 were dead before the end of the second year of life. Even in a large up-to-date city like Johannesburg, it is estimated that the infantile mortality rate is well over 200 per 1 000 live births. I say 'estimated' advisedly, because this country has not yet realised in practice that compulsory registration of births and deaths for all sections of the community is the first step in any intelligent public health programme.

Two main factors may be immediately related to this wholesale destruction of human infants. The first is congenital malnutrition and the second is connected with several problems of weaning. Congenital malnutrition expresses itself in African infants firstly, as a low birth weight, usually $\frac{3}{4}$ lb. on the average less than that of white infants, secondly as a very low iron con-

cent of the liver, from 10 to 30 times less than in the case of the white infant, and thirdly as foetal and neonatal rickets.

A low birth weight even in favourable circumstances can frequently affect the later developmental history of the infant. Where the mother is also chronically malnourished, this becomes a more serious difficulty especially in the case of pellagra which is endemic in Johannesburg and other parts of South Africa. The older Italian investigators have repeatedly stressed the deleterious effect of nurturing infants on breast milk derived from pellagrous mothers (Lavinder and Babcock, 1910; Weston, 1945). This view we can confirm from our own experience, for we have noted the occurrence of infantile pellagra and of severe rickets of infants while still at the breast.

In this connection, too, I might add that in our small series of 52 cases of pellagra in infants where we have been able to collect reliable information, we have discovered that 36 of these pellagrins were born between September and March, the period of the year when pellagra is most prevalent in Johannesburg. Only seven of the fifty infants were born between May and July, that is when pellagra is at a minimum. Children born during the pellagra season are at a serious disadvantage, firstly, because the period of maximal intra-uterine growth takes place when the mother is more likely to be suffering from an acute or subacute attack of pellagra and, secondly, the early months of life of the infant are spent at the breast at a time when another acute attack is impending in the early autumn months. It is not surprising therefore, that we should have encountered several cases of pellagra in infants while still at the breast.

Having survived the first year of life, the child experiences another serious set back at weaning; even when there are no gross deficiency signs, it is common knowledge that weaning constitutes a critical period in life even amongst better fed European infants. As far as the African women are concerned, ignorance of the most rudimentary knowledge of infant feeding coupled with the inability to purchase food best suited to infants, mean that the baby will be weaned from the breast for the most part on to a type of gruel, prepared by boiling corn meal in water or diluted

milk. The particles are strained off and the infant is fed the milky, slightly granular fluid. Such a diet obviously cannot sustain an actively growing child. Even healthy children, endowed with excellent nutritional reserves, can hardly be expected to remain alive and well on the types of diet usually fed to African infants. Hence, the very heavy mortality reported during the second year of life. Weaning is a problem common to all the native peoples throughout the entire African continent. Thus Johnstone (1924) reported that 72 % of infant deaths in Kenya occurred during the first year of life and 21 % were noted between 9 and 18 months which corresponds to the period of weaning. In this part of Africa, the infantile mortality rate is similar to that reported from the Transkei in South Africa.

The School Children.

Virtually no statistics are available of the health of the child from the time of weaning until it enters school. That the human erosion steadily continues, however, is reflected by the several health surveys conducted amongst school-going children in different parts of the country during the last ten years. These surveys reveal that South Africa, through negligence or apathy, is dangerously neglecting her human assets (Union Year Book, 1941). In 1939, it was shown that amongst 72 000 white children, defects of a major or minor nature were found in different areas to fluctuate between 32.7 % in the Natal province to 87.3 % in the Orange Free State. The incidence of malnutrition was, on an average of 93 per 1 000 children, as compared with 11.1 per 1 000 for England in 1933. Amongst 7 000 native school children surveyed in different parts of the country, Kark and Le Riche (1944) detected gross malnutrition in 23.4 % in some areas and 75.6 % in others. These two investigators stressed that these figures did not reflect the true gravity of the situation because only the economically more settled families are able to send their children to school. Later, le Riche (1943) and a team of medical students surveyed a native township six miles from the centre of Johannesburg. Le Riche concluded that 50.6 % of these children were in need of medical attention, while 9.7 % required urgent treatment in hospital.

Amongst the children of mixed parentage, the situation is equally serious. In the Cape, Brock and Latsky (1942) demonstrated that 47 % of the coloured children were malnourished. In addition, surveys from other parts of the country have shown that 35 % of European and 88 % of African children are suffering from schistosomiasis. In malarious districts, the splenic index amongst African children may be as high as 78 %.

Comment.

The valuable surveys have served to supplement the hopelessly inadequate health inspection, whereby a school-child is inspected only once in seven years. Any defects observed are referred to the parents who are then obliged to consult their family doctors. The children of the poor families, therefore, with seemingly minor defects, for the most part remain untreated and consequently over a period of years, small defects are progressively magnified and in this way increase the burden of national ill health.

At the present moment, there are 17 pediatricians to attend to the health of 4 million children. This is one of the reasons why so little attention is devoted to child welfare, for pediatricians, as a general rule, are no less aware of their social responsibilities than are public health officers. Even in the medical schools, pediatrics is a much neglected part of the students training. Only this year has the medical faculty of the University of the Witwatersrand recognised the need for providing facilities for the training of pediatricians.

While South Africa has accepted the Constitution of the new Health Organization and officially subscribes to the view that

«The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition,»

in actual practice, neither the European nor the African children enjoy the benefits of such a progressive philosophy. The general backwardness of the people and widespread chronic malnutrition allow for the persistence of such serious communicable diseases as amoebiasis, tuberculosis, typhus, schistosomiasis and malaria.

This offers a potential threat to other more advanced countries as demonstrated during the last War, where thousands of American and British troops contracted one or other of these different types of diseases in endemic areas where they were stationed. It is therefore quite clear why the Constitution of the New Health Organization states that »unequal development in different countries in the promotion of health and control of disease, especially of communicable disease, is a common danger».

The health of the people is indeed the concern of the people themselves. Health cannot be imposed upon a people. The people themselves must learn to press for health and social advancement. It is only among an enlightened population that health and social progress are *demanded* by the people.

The growing consciousness of their economic backwardness and dissatisfaction with their present subservient state cannot fail to find expression in the near future in the emancipation of this great mass of African people. Such a mass movement as is now developing in this country will inevitably lead to steady pressure for a general economic improvement together with all the accompanying amenities, with better educational facilities and the demand for curative and preventive medicine.

In summarising the situation in South Africa, it may be stated that in comparison with the European, the African and the coloured peoples are ten times poorer, ten times less is spent on their education, the infantile mortality rate and the death rate from tuberculosis are ten times greater and the average expectation of life is approximately half that of the European.

It is not without some understanding of the world situation that Bernal (1939) was led to state:

»We have in the world today, a number of palpable material evils — starvation, diseases, slavery and War — evils which in previous times were accepted as part of Nature or as the actions of stern malevolent gods, but which now continue solely because we are tied to out of date political and economic systems . . . War in a period of potential plenty and ease for all is sheer folly and cruelty. The greater part of disease in the world today is due directly or indirectly to lack of food and good living conditions. All these are plainly remediable evils, and no one can feel that science has been properly applied to human life until they are swept off the face of the earth.»

In conclusion, I cannot refrain from expressing my humble opinion that the greatest anti-health factors in South Africa are the vicious man-made environment and race prejudice, both of which deny to the coloured people the right to social and economic self-betterment.

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CO-RELATOR.

Nutrition.

By **P. Plum**, Prof., Copenhagen, Denmark.

I am going to say a few words on celiac disease. I am doing so supposing that some aspects of this syndrome might be of interest in a general discussion on nutrition.

First I should like to make clear what I mean by celiac disease. I refer to the classical clinical picture of a child most often between six months and three years old, thin, with poor muscles, flat nates, a big, protuberant abdomen, with asad expression, low blood sugar curve after oral ingestion of glucose, impaired absorption

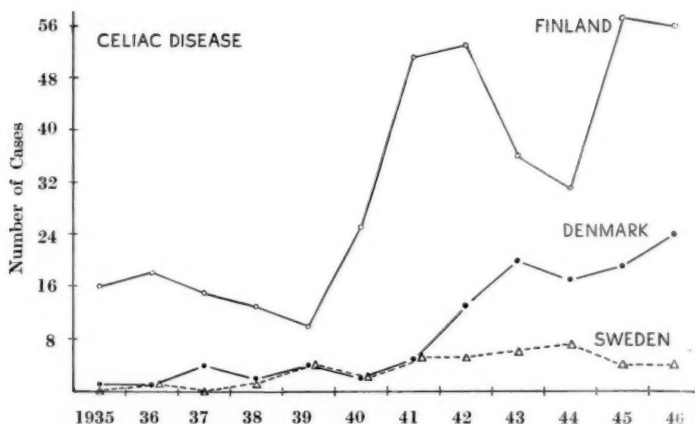


Fig. 1. Frequency of celiac disease in some of the Scandinavian countries before, during and after the last war.

of fat which is split in the normal way and with a characteristic X-ray pattern of the small intestines. In Denmark the so-called «secondary» cases of celiac disease seem to be only a small fraction of the total amount of cases, therefore I am only referring to the so-called «primary» cases.

By the way, I can mention that in 90 per cent of our classical «primary» cases we found that there would be either more than 5 per cent of fat in the native feces or excreted more than 10 per cent of the fat ingested in four days experiments.

I will restrict myself to mentioning a few points that might be of interest to the general problem under discussion today.

The frequency of the disease seems to have changed in certain Scandinavian countries during the last war.

Slide No. 1 shows the frequency in Finland, Denmark and Sweden, before, during and after the last war. You will see that in Sweden the figures are nearly unaltered, while there is a considerable increase in Finland and Denmark. From Norway I have got the information that they have had $2\frac{1}{2}$ times as many cases during the five year period 1941—1945 as in the preceding five year period. The increase in Denmark is not due to improved

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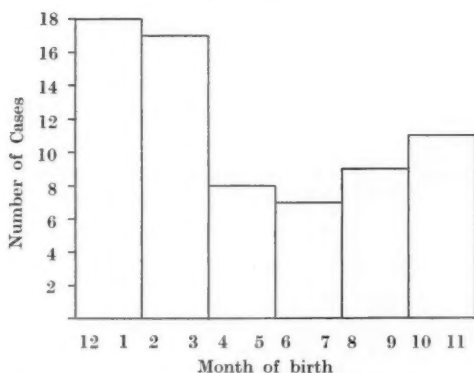


Fig. 2. Month of birth of children with celiac disease in Denmark.

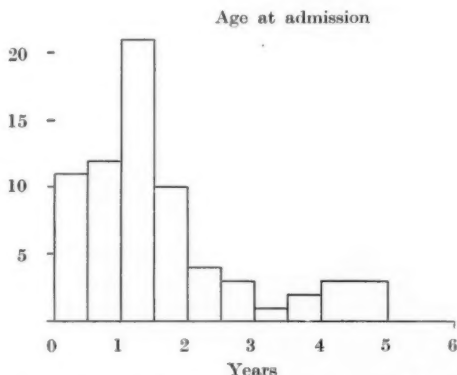


Fig. 3. Age of children with C. D. at admission.

diagnosis. We have been through all the case trends though all these years and have found only one or two per year.

A seasonal distribution is not very pronounced but as you will see in slide No. 2 more children with c. d. were born in Denmark during the winter months, November, December, January, February, than during the summer months. The slide comprises 70 cases altogether.

It is nearly impossible from the case records to make sure in

which months the symptoms started, because the disease often begins insidiously.

The age distribution is shown in the next slide.

It will be seen that only about one third of the children were less than one year on admission.

The children often stayed in the hospital for a long time.

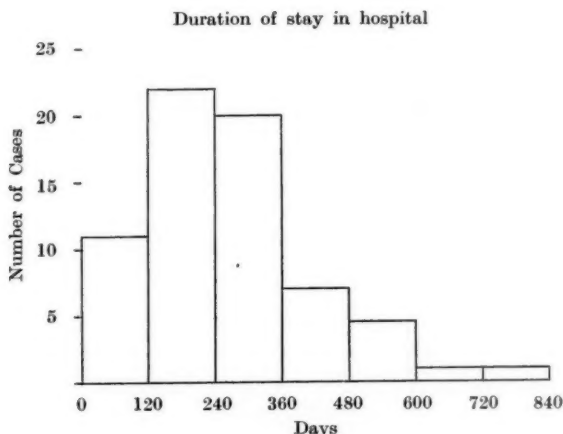


Fig. 4. Duration of stay in hospital.

Slide No. 4 demonstrates that most of our cases were severe. In more than half of the cases the children stayed for more than eight months in the hospital.

The nutrition prior to the disease is of some interest. At the age of two months only 20 per cent of the celiac patients were on breast milk or on breast milk plus formulas. In Denmark 80 per cent of normal children are on breastfed or breastfed plus artificially fed at two months of age.

It is well known that the pathology has most often been found negative. I shall only take a brief comment on the flat blood sugar curve, namely that we have found that there seems to be a parallelism between the time of emptying of the stomach and the flatness of the oral blood sugar curve, a fact that corresponds

well to the findings of Macy and McQuirry that a duodenal application of the sugar often is followed by a less flat curve. We made the same observation at the time the reports from Boston were published. The recent important studies of the duodenal contents I will not comment upon.

Occasionally we have investigated the x-ray picture of the small intestine in c. d. since 1936, but it was not until Ross and Golden had reported their most interesting studies that we took up the problem. Since 1941 we have subjected all cases of celiac disease and a big number of other cases to x-ray examination of the small intestine using the following technique: without previous meals ingestion in the morning of pure barium sulphate in water, exposures being made after 40 minutes and 1, 2, 3, 4, 5, 7, 8 and 24 hours after the barium meal. Four hours after the barium meal the child is given its ordinary meal.

In cases of C. D. we have found that the most characteristic feature is a combination of hypertonicity and hypotonicity.

With regard to the question of the specificity of these x-ray changes we have come to the conclusion that the pronounced x-ray changes must be considered highly significant diagnostic evidence, but they are not pathognomic. We have found these changes in many cases which were not classical cases of celiac disease, but which clinically had to be diagnosed as mild or abortive cases.

I should like to mention that we have found the typical c. d. x-ray changes of the small intestine in a number of cases of dwarfism and of rickets without intestinal symptoms, as a probable explanation of the growth retardation and the skeletal changes. In these cases the fat absorption and the glucose absorption curve were found abnormal too, in other words, we have by means of the x-ray examination found cases of celiac disease with complications but with no intestinal symptoms.

From the physiology we have learned how important the normal peristaltic movements of the small intestines are to the absorption. So we seem in the x-ray findings to have found a visible immediate explanation of the impaired absorption in C. D. But the Roentgen findings do not give an explanation of the cause of this motor disturbance of the small intestine.

ROENTGEN DIAGNOSIS.

	No abnorm- ality	Enteritis	Colitis	Possibly Celiac Disease	Celiac Disease	Total
No dyspeptic symp- toms	32	1	0	0	0	33
Nervous vomiting, anorexia, colica ..	37	4	0	0	0	41
Constipation	16	3	0	0	0	19
Colitis	18	7	8	0	0	33
Chronic nutritional disturbance, dys- pepsia chronica ..	17	34	1	20	5	77
Atrofia infantilis...	0	1	0	1	3	5
Possibly celiac di- sease	0	0	0	16	4	20
Celiac disease	0	0	0	3	72	75
Dwarfism	18	2	0	2	0	22
Rickets	1	1	0	2	2	6
Total	139	53	9	44	86	331

Fig. 5. Comparison between the clinical and the x-ray diagnosis in 331 cases.

Reconsidering the points mentioned we might first ask the Roentgenologist what he thinks is the etiological mechanism of the motor disturbance described; is it allergic, toxic, infectious or deficiency manifestation? I think he would refer to the resemblance between the x-ray findings in c. d. and in what has been described as chronic nutritional disturbance.

Reconsidering the frequency of C. D. in the Scandinavian countries during the war it seems reasonable to look for a deficiency of nutrition. Sweden was not in the war and the frequency was not altered very much there. Denmark, Norway and Finland were occupied and in war and the C. D. frequency increased to a considerable degree. The most important nutritional element common to children of this age is cow's milk. We would now ask the question: Did the cow's milk undergo any changes during these years? We do not know but we do know that the food of

the cows was altered, the import of concentrated cow's fodder being stopped in Denmark at the German occupation in the spring of 1940. A danish cow used to have about 1 000 pounds of concentrated fodder a year, mostly during the winter consisting of cotton-seed cakes, 38 per cent, cocoanut cakes 15 per cent, soya cakes 15 per cent, sunflower cakes 12 per cent, linseed cakes 3 per cent, rape cakes 1 per cent and other oil cakes 2 per cent. Among the constituents of these cakes may be mentioned unsaturated fatty acids, folic acid and other members of the vitamin B group. Of course the possibility of unknown factors of importance to the normal function of the intestines should be considered too.

Our results with treatment with liver extract and the vitamins B have not been convincing. Our experiments with folic acid are too limited to allow of any conclusion.

If composition of the cow's milk should be of any importance to the frequency of C. D. in Denmark during the war it should be expected that the tendency should be most pronounced during the winter time because the cows have plenty of green fodder during the summer months, when their food therefore should be sufficient.

As you remember more children with celiac disease were born during the winter months in Denmark a fact which might be related to the altered composition of the cow's milk, but which of course, might have many other explanations.

Our studies along these lines have not been concluded, but I think it will be interesting to hear about the possible experiences from other countries about the nutrition during the war and the frequency of C. D. In this way, perhaps, we might be able to get some suggestion that might enable us more successfully to look for the etiology of this fascinating disease. At the same time probably getting some new knowledge of the intestinal physiology.

CO-RELATOR.

Some Statistical, Clinical and Experimental Data on Malnutrition in Greece.By **G. Logaras**, M. D., Athens, Greece.

The starvation in the enemy occupied countries of Europe is a well known fact. The population of Greece has suffered from hunger from May 1941 on. It should be borne in mind, however, that even before the war Greece was not a well fed country. A very small percentage of the soil is suitable for agriculture and the fertility of the land is very poor.

The diet of the people was deficient not only from a qualitative point of view but also in energy value. Dietary surveys carried out in 1938—39 showed that in 29 % of the small income families the daily energy value of the diet amounted to less than 2 000 calories per man. But it was more deficient from a qualitative point of view, i. e. in first class protein and vitamin A. The total amount of «visible» fat was made up exclusively of olive oil. The consumption of fresh dairy butter was very small. The bulk of the diet consisted of bread, pulse and farinaceous foods. The daily consumption of bread per person varied from 224 to 697 gm., averaging 384 gm. The budget for food in the families under study amounted to 40—70 % of the family income. This evidence of poor nutrition was reflected in the public health statistics. The average length of life was short (49 years). Rickets was not an infrequent disease. Some regions of Macedonia showed a certain number of cases of pellagra yearly. Night-blindness and xerophthalmia were not rare.

As mentioned before, Greece has never been self-sufficient as far as food goes. During the occupation by the Germans food imports ceased and from the local production of foodstuffs — restricted as it was — a large proportion was taken for the occupying armies. In consequence a country-wide famine started in June 1941 which killed a great number of the urban population. One gets a rough idea of the extent of starvation from a diagram illustrating the energy value and the protein content

of the rations distributed in Athens and Piraeus during the war years.

On behalf of the Joint Red Cross Committee, I carried out during the occupation of Greece 6 dietary surveys twice a year in 600 families of Athens and Piraeus.

The worst period of the famine in Greece was between November 1941 and February 1942. During this period the daily ration per person was as follows: November 183 calories, December 410, January 1942 356 calories, February 204 calories. The rest was purchased in the black market at exorbitant prices. Of the total number of families surveyed at that period, 17 obtained less than 1 000 calories per man per day and 9 less than 1 700 calories per man per day. The variety of consumed food was extremely restricted. The bulk was made up of vegetables and fruits. Lemons and oranges were eaten by all families. Cheese and meat were absent from the menu. A small amount of fish was consumed by some of the families. The daily intake of protein varied from 7 to 56 gm. per man.

The results of the above diet were hunger oedema and increased mortality independently of other diseases or epidemics. In the localities where exact data in the form of actual statistics was available the number of deaths increased $5\frac{1}{2}$ times. At the same time the numbers of births per month decreased in Athens from 1 500—2 100 (prewar level) to 700, 600 and 423 in September 1942. The infant mortality in Athens and Piraeus increased from 458 in January—March 1941 for the ages 0—4 years to 1 213 for the quarter October—December and to 1 554 for the quarter January—March 1942.

During this period an epidemic of pellagra broke out in Athens and Piraeus. In November 1941 cases of classic pellagra appeared and in the month of March 1942 amounted to 3 000 to 4 000. The school age children were especially affected by this deficiency disease. In the month of April 1942 we examined 1 224 children in 9 elementary schools of Piraeus for symptoms of pellagra. 253 of them (i. e. 20.67 %) showed dermal lesions. There was also a severe deficiency in the supply of vitamin A. This is shown by the measurements of dark adap-

tation we carried out in 294 adults. According to the adaptometer described elsewhere 113 of the 249 subjects examined between August and September 1942 showed dark adaptation impairment and of these 26 showed night blindness. As the total intake of vitamin A in the food was exclusively carotene from vegetables and the amount of fat in the diet was extremely low, we wished to determine whether a supply of 80 gm. of olive oil per person per day for a period of 2 months would influence the dark adaptation curve favourably. The result was negative. In contrast to this, the improvement in dark adaptation was striking in 7 of the 8 subjects to whom vitamin A concentrate (total amount 360 000 I. U.) was administered for a week. The cases of night blindness in the population persisted for the next year with more severe symptoms compelling the patients to consult ophthalmologists. Somewhat better provided with vitamin A were the children in the ages between 8—14. Of 99 children tested by this same method in 1943 only 17 showed any dark adaptation impairment. This is to be explained by the fact that parents deprived themselves for their children and even supplemented their diets when possible from the black market.

After the end of 1942 some slight amelioration of the diet of the people was noted, due to shipments of food from Canada and the United States which were distributed under the supervision of the Joint Red Cross Committee. A dietary survey of 207 working class families during the period January—April 1943 showed that the nutritive value of the diet of only 43 families could be regarded as adequate according to the League of Nations standards. In 48 additional families the energy value of the diet ranged from 2 000 to 24 000 calories per man per day. 52 families were receiving less than 1 800 calories per man per day. The diet was deficient in animal protein because of the low consumption of meat, eggs, cheese, fish, etc. Only 17 % of the working class families were consuming any meat, 22 % fish, 6.9 % cheese and 6.8 % eggs. The consumption of »visible» fat increased and was reaching the prewar level. Of the total number of 207 families, only 6 were not consuming any visible fat. 59 % of the energy value of food consumed was derived

from the food distributed by the Red Cross. 41 % was purchased in the black market at very high prices.

These families were also surveyed clinically. Subjects of all ages seemed older than their years. Not only was the skin of the children lacking in elasticity but even their hair was in some cases dry, coarse and grey. The body weights of all ages were low. Serum protein estimated on some subjects was below the normal range. Tuberculosis incidence was noted in 5 % of the persons examined by X-ray. Hemoglobin according to Sahli was 71—100 % in 47 % and 61—70 % in 45 % of the subjects. 15 % showed anaemia with an associated number of erythrocytes under 3 500 000.

The diet in institutions for children at that period was not any better. During the 2 month period beginning September 1943 we carried out a nutrition experiment in a girls' orphanage in Athens. The average age of the girls was 12 years 4 months. The energy value of the food consumed was 1 536 calories per day. The protein intake was 56.3 gms. daily but only 10 % was derived from animal sources. On this diet the girls increased in body weight during the 2 month period by 480 gm. with standard deviation 1 282 and 205.2. But the inadequacy of the above diet is well demonstrated by the following experiment. When it was supplemented by 430 calories in the form of whole wheat bread or biscuits containing 15 % animal protein, there was an increase in weight of 1 234 gm. (s. d. 1 072 and σ 140) for the bread group and 1 069 gm. (s. d. 860 and σ 101) for the biscuit group, respectively.

The increase in height in the basal diet group was 0.628 cm. (s. d. 0.91 and σ 0.146), whereas in the bread supplemented group it was 1.07 cm. (s. d. 1.08 and σ 0.17) and in the biscuit supplemented group 1.1 (s. d. 1.3 and σ 0.153). This small scale nutrition experiment in 171 girls demonstrates the deficiency of the diet and its immediate effect upon the stature of the Greek children.

By the end of 1943 the U. S. shipments of food had increased and a further slight amelioration of the food situation was noted. 110 small income families were studied in Athens and Piraeus

during November—December 1943 and 112 families between January—June 1944. There was not any striking difference in the diet during the 2 periods of this survey. Altogether 180 families obtained in their daily diet less than 1800 calories per man per day. Only in 25 families was the energy value of the food consumed in the range of 2 000 to 2 600 per man per day. The protein intake was still unsatisfactory. Consumption of animal protein was especially low. Only in 18.2 % of the families was meat consumed. The fat intake amounted to 13.14 % of the total calorie intake.

In general the effects of the famine period on the children of Greece are shown from somatometric data collected by the Swiss Red Cross in 1942—43 and the Social Insurance group 1 year later. Some of these data were analysed by Dr. Valaoras (see *The Milbank Memorial Fund Quarterly*, Vol. XXIV, July 3, 1946 pp. 215—234).

In the first survey 55 764 children in all were examined. These children measured in 1942—43 were somewhat taller but their weight was less than that of similar age groups measured in 1927—28. In the second survey made by the Social Insurance Group in 1944—45 a total number of 75 000 children aged 1 to 15 years was examined and a decrease was noted in the average heights for children 8 to 14 years of age. The group 12 to 14 years of age was shorter even than the 1927—28 standard. The von Pirquet Pelidisi index was normal in both surveys for the children in the first 2 or 3 years of age because of the efficient distribution of milk and other food. The index drops for older children and reach the lowest point at the age of 10 to 12. It is worth mentioning that the worst undernourished children were between 7 and 14 and in the year 1944, 55 % showed Pelidisi index below 96.

Since the liberation of Greece the food situation has been slowly ameliorated, especially through UNRRA shipments. But vulnerable groups not reached by organized supplementary feeding programs continue to show the effects of chronic malnutrition. Dr. Albert Mendeloff of UNRRA reported an increase in size,

osseous deformities, chronic rickets, skin changes associated with vitamin A, gingivitis, still births, premature births, etc.

The nutrition problem in Greece is chiefly an economic problem and taking into consideration the long period of inadequate nutrition and the ordeal of the war year, rehabilitation from the public health point of view will be a long procedure.

CO-RELATOR.

Nutrition.

By **Dag Riis**, M. D., Oslo, Norway.

During the years before the last war a great effort was made in Norway to convince people of the importance of optimal nutrition. As an example of this the Oslo School breakfast, instituted by professor Schiøtz, may be mentioned.

The war made a complete change in the food situation in Norway and consequently limited severely the number of food articles that were available. Fortunately the danger of the situation as far as nutrition was concerned was well understood by most parents.

To secure the requirements of the first growth period, including fetal life, infancy and the first 6 years, this period was given special attention and the protective foods available were distributed accordingly. That is to say, pregnant women and nursing mothers, infants and pre school age children were given 750 ml of milk and 5—10 gm of cod liver oil daily. To meet the calcium requirements 0.4 % of calcium carbonate was added to the bread, which consisted of barley, rye and oats milled to 95 per cent.

The caloric intake from rationed food was sufficient during the first growth period.

During the school age, however, the caloric intake was too low. Besides this caloric deficiency the children as a whole suffered from lack of valuable foodstuffs such as meats and dairy products and particularly fresh fruit and vegetables. The vitamin C intake was low and was chiefly dependant upon the supply of kohlrabi and potatoes. Potatoes were in fair supply, except

in one year when kohlrabi had to be substituted. Otherwise salted herring or salted or smoked fish of a poor quality were the foodstuffs making up the hot meal of the day. (The ration of bread during childhood varied from 100 to 200 gm. Fat and sugar amounted to 30 gm daily. Fat was given in the form of butter or margarine.)

The food articles were very irregularly supplied even if the rations as a whole were fairly covered.

The great problem for the pediatricians was to teach the mothers how to utilize the foodstuffs available in order that the minimum requirements might be covered. This was performed mainly through the many infant welfare centres erected in Norway by various charitable health organizations. In Oslo the first municipal welfare centre under the name of Sagene Health Station for Mothers and Children, with dr. Utheim Toverud in charge, was erected in the year 1939, serving one fourth of the population of the city.

At this centre a systematic health supervision was given to pregnant women, nursing mothers, infants and pre school children. Besides the usual physical examination, determinations of bloodcalcium, vitamin C and hemoglobin were performed to check the results of the supervision. During pregnancy cod liver oil and brewers yeast were given as constant additions to the diet and during the last three weeks vitamin K as well. The importance of breast milk till the age of 9 months was emphasized, resulting in more than 80 % of women feeding their babies for this period at least partly. Mothers who had not been so supervised showed a somewhat lower percentage of breast feeding.

Simplicity has been the outstanding feature of the artificial feeding of infants in Norway during the last 25 years, in accordance with the principles advocated by professor Frølich since 1922. A mixture of equal parts of milk and water with 7 per cent cane sugar added was given during the first 6 weeks, later 2/3 milk and water with about 4—5 per cent cane sugar and varying amounts of extract of malt till the age of 6 months. Cod liver oil and orange juice were added early.

The infant mortality in Norway has been very low, which

has been taken to indicate that the infant feeding was satisfactory. This situation proved to be of great advantage when the war broke out. At the Sagene Health Station the infant feeding has been even more simplified. $2/3$ milk and water with 4 per cent cane sugar was given with good results from the first visit of the infant, at 2—4 weeks. Cod liver oil was given to all infants from the age of 2 weeks, and from the same time on vitamin C was given, in the form of the juice of raw or cooked kohlrabi or the juice of hips and haws (i. e. the fruit of the rose bush and hawthorn), and when available tomatojuice was also given. At the age of 4 months purée of cooked and strained vegetables, mostly carrots or kohlrabi, was given. All premature infants received a small addition of reduced iron from the age of two months and did not develop anemia.

In the feeding of the pre school child the great difficulty was to make the food appetizing. This applied particularly to older children who had developed definite eating habits before the situation changed. At Sagene Municipal Health Station demonstrations of the preparation of food were given regularly once or twice a week in order to help the mothers.

As has been said, a definite caloric deficiency existed as far as the school children were concerned. For the 7 year old child a deficiency of about 100 calories daily was calculated, increasing to about 1 300 calories for children of the age of 12—15 years. During the war the school breakfast was abandoned and only cod liver oil and kohlrabi or synthetic C vitamin were given. The nutritional condition of the school children was rather poor during the years 1942—1943. Fortunately in 1943 relief organizations in Denmark and Sweden started distributing various forms of soups which proved to be very valuable.

In trying to judge the influence of the nutrition on the health of the children various interfering factors have to be considered. The housing conditions during the war were very poor. Soap and hot water were scarce, resulting in a greatly increased occurrence of various skin diseases like scabies and impetigo. Epidemics of contagious diseases prevailed during the whole war time, and

the nervous strain under which the population lived showed its influence in various nervous symptoms both among parents and children.

The infants were in good nutritional condition with no signs of deficiency diseases. Cases of clinical rickets have been very rare in Norway for many years. This situation is probably due to the extensive use of cod liver oil, which in Norway is considered as food and not as a medicine. The few cases of rickets which were admitted to the University clinic during the war occurred in children of peasants who did not get a ration of cod liver oil, but who had a plentiful supply of milk.

In the pre school child a close supervision of the condition of the teeth was kept at the Health station in order to follow the results of the program on the incidence of caries. We wish to emphasize that the diet was regulated to supply as far as possible the calcifying factors as well as to reduce the local caries producing factors. In the children supervised from fetal life and infancy a reduction of up to 50 per cent occurred compared with children supervised after infancy.

As far as the school children are concerned records from the Health Department of the City of Oslo (Chief: Dr. med. Z. Stoltenberg) show that the average height of the children which had shown a steady increase during the years preceding the war, remained unchanged or even decreased during the war time.

The state of nutrition judged according to the Rohrer's index indicated a decrease for boys and girls in the public schools throughout all grades, which was most pronounced in children where the caloric intake was calculated to be at its lowest.

In the school children the incidence of caries decreased during the war. In the 7 year old child 85.6 caries centra pr 100 permanent teeth was registered in the years 1939/40, compared with only 38.6 centra pr 100 permanent teeth for the years 1944/45.

As far as tuberculosis is concerned it may be of interest to mention that though the incidence of positive reactors among the school children in Oslo did not increase during the war, the number of cases of active tuberculosis did.

The high content of cellulose in the war time food very often

produced symptoms of colitis and especially fermentative dyspepsia whereas cases of constipation were rarely met with. After the war the diarrhoea has practically disappeared, and constipation is now a very common occurrence.

Generally it may be said that the health condition of the Norwegian infant during the war was good. The nutritional state of the pre school child was satisfactory, although their feeding gave rise to many problems.

During school age, however, a caloric deficiency was present, and a marked decrease of the weight/height proportion was recorded.

What I have said refers particularly to the children of Oslo, but it is probably valid also for the children of the other towns in Norway, whereas the children of the peasant population were in a potentially more advantageous situation.

Slide 2. This slide shows the Rohrer's index for boys in the public schools of Oslo. The lower curve represents the index from 1943, the higher one the index from 1935, which I have here chosen as a representative for the prewar indices. The respective diagrams covering the years 1925, 1930 and 1940 have here been

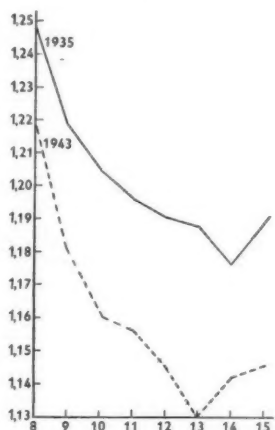


Chart I. Rohrer's index. Boys.

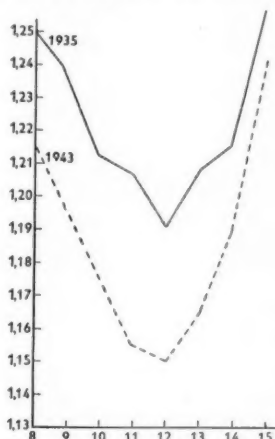


Chart II. Rohrer's index. Girls.

omitted for the sake of clarity and on account of being nearly similar.

Slide 3. This slide shows the Rohrer's index for girls in the public schools. The lowest point on the curve for 1943 corresponds for the boys with the age of 13 years, for the girls with the age of 12 years.

Discussion.

Dr K. G. Chaudhuri, Calcutta, India: *Nutritional disorders following Gastro-enteritis in children.*

We come across certain types of post-diarrheal nutritional disorders which appear to form a distinct clinical entity. The disease picture is characterised chiefly by edema, anemia, petechial hemorrhages, changes in the skin and mucus membrane, failure of growth and some other associated symptoms.

Usual history is that the children suffered for a long time from diarrhea, the cause of which may be dietetic, infectious, or otherwise. Feeding history is also significant. The children are prematurely weaned, given artificial food, usually barley or other cereal water. The age range of these cases is between 1 and 9 years, the peak age of incidence being $2\frac{1}{2}$ —3 years. There is no predilection for any sex.

Following the diarrhea which may last for four weeks or so edema starts in the lower limbs and spreads to the scrotum, upper limbs, face and abdomen. Pleural and pericardial effusions are rare.

Anemia is marked. Hemoglobin value varies from 15—50 % (Sahli). Erythrocyte count is between 1.1 and 3.5 mill. Sometimes anisocytosis and nucleated erythrocytes may be present. Anemia is of macrocytic type.

Petechial hemorrhages occur mainly on the trunk and recurs frequently.

Very complex cutaneous changes are observed. Black patches appear in the limbs and abdominal wall and exfoliate giving rise to scaly desquamation. The skin underneath is shiny, smooth and pale colored. Septic foci in these areas are common. Cutaneous changes are not confined to the exposed surfaces as in pellagrins. Mucus membrane of the mouth, around the nostrils, canthus of the eyes, anus, prepuce and labia is denuded and appear sodden. Magenta discoloration or fissuring of the angles of the mouth characteristic of riboflavin deficiency is not usually noticed. Hairs are brown, unlike the dark black colour of Indian children and devoid of gloss.

Wasting and failure of growth is profound but disguised by the edema. When the edema disappears the child is seen reduced to mere

bone and skin with caved-in chest and protuberant abdomen. One child 4 years old weighed only 13 lbs. 11 oz. with edema and 12 lbs. 9 oz. when it disappeared. His height was only 32".

The general appearance of the children is wretched; they are irritable, show photophobia and bury their head in the pillow. They are fatigued, cheerless and often moan. Muscles are markedly hypotonic. Fever is rare; diarrhea or constipation may be present.

Physical examination does not show anything abnormal in the chest. The liver is frequently enlarged; the spleen is sometimes enlarged associated with intercurrent malaria or kalazar infections. Prognosis is grave, 9 of 32 cases died. Careful nursing and proper diet are very essential. Crude liver extract with Vit. B complex, orally and parenterally, iron, glucose infusion and blood transfusion are very beneficial. Protein hydrolysate has also been used with benefit.

LABORATORY FINDINGS:

Table 1. *Blood Chemistry.*

(Minimum and maximum figures are given)

Serum albumin	2.8—3.9 Gm%
Serum globulin	2.1—2.9 Gm%
Urea	14—15 mgm%
N. P. N.	28—45 mgm%
Cholesterol	28—45 mgm%
Chloride	436—467 mgm%
Sugar (Fasting)06—.08 mgm%

Table 2. *Glucose Tolerance Test*

After ingestion of 30 gm of glucose orally

Fasting080—.095 mgm%
After 45 min.095—.133 mgm%
" 90 "095—.125 mgm%
" 135 "085—.117 mgm%
" 180 "080—.105 mgm%

Platelet count, coagulation and bleeding time are all normal. Leucocyte and differential count show no abnormality. Fragility test normal.

Urine — only a trace of albumin occasionally. Water concentration test normal. *Stool* — *B. Coli*, salmonelle group of organisms in culture, *giardia lamblia*, *ascaris*, *trichomonas*, whipworm found. *Entameba histolytica* rare.

DISCUSSION:—

It appears from the results of investigation that the diarrhea might originate from any cause and the subsequent course is independent of the etiological factors. There is depletion of serum proteins specially of serum albumin. Bose found during Bengal famine that the normal albumin globulin ratio of 2:1 is reversed in famine edema. In these cases the serum albumin is also low. But famine edema is not associated

with an enlargement of the liver and macrocytic anemia. Beri-beri edema is accompanied by cardiac changes. Therefore, this edema cannot be attributed to famine or beri-beri, neither is it due to kidney or cardiac condition.

Anemia is of macrocytic type unlike that of beri-beri or pellagra which is of normocytic or microcytic type. Possibly it is due to the absence of anti-anemic factors as in sprue. Whipple and Robscheit-Robbins showed that hypo-protenemia is always associated with a low reserve store of hemoglobin producing factors in the liver.

Petechial hemorrhages are not due to thrombocytopenic purpura. There is no hemolytic tendency as the fragility test, coagulation and bleeding time are normal. It may be due to deficiency state and changes in the capillary tension.

It is difficult to explain the cause of complex skin condition. Some simulate pellagrins, others riboflavin deficiency, but no definite etiological factor could be determined.

The failure of growth is profound; lack of vigour, hypotonicity of muscles, and fatigue are most prominent, and is a direct result of chronic inanition.

Carbohydrate metabolism is also affected. Bose thinks it is due to the failure of absorption in the alimentary canal. Flattened glucose tolerance curve, however, is suggestive of hepatic insufficiency and the enlargement of the liver should be considered in this context.

Trowel described a similar syndrome occurring in African children and thought it to be a clinical variant of pellagra. Later he changed his opinion and described it as «*Kwashiorkor*», a type of malignant malnutrition characterised by edema, fatty liver, skin changes, steatorrhoea, deficiency bowel pattern, and decreased plasma albumin and increased plasma globulin occurring in Tropical Africa.

The clinical picture is perhaps the summation effect of prolonged and severe underfeeding due to low intake of food, failure of absorption, or increased elimination of vital products through chronic diarrhea. Once it is produced it may be associated with frank deficiency diseases but more commonly with subclinical varieties of deficiency. It is a pattern of nutritional disorder affecting mostly underfed children of low income groups in tropical countries.

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Dr. Carlos Krumdieck, Lima, Peru (no manuscript received).

Prof. M. S. Masloff, Leningrad, USSR; *La pathogénie des états toxiques, septiques et dystrophiques chez les enfants.*

Les ennemis principaux de bas âge sont moins les maladies gastro-intestinales, pneumonies et méningites que les états toxiques, septiques et dystrophiques, qui les accompagnent. Si nous voulons consciemment combattre la mortalité des enfants en général et lutter contre la léthargie en cas des maladies isolées nous devons au premier abord apprendre à combattre ces états toxiques, septiques et dystrophiques, à devancer leur apparition et paralyser leur influence pernicieuse sur l'organisme.

Les savants de l'Union Soviétique étudient ces états depuis plusieurs années. G. N. SPERANSKY (Moscou) a élaboré et argumenté l'étude de soi-disant «Anneau septique» où tombe l'enfant atteint de toxicose. Ses collaborateurs ont étudié l'état de sensibilisation et de réactivité des enfants en état toxico-septique. Par de nombreux travaux de ses collaborateurs (Moreff, Mouravina, Katz et d'autres) les particularités de biochimisme du sang et de métabolisme du temps des toxicoses ont été étudiées à fond et les troubles considérables ont été démontrés dans les régions de métabolisme-hydrominéral, azoteux, carbohydrate, graisseux, vitamineux ainsi que le trouble de la balance acide-basique (acide-alcalin). CHAFFERSTEIN (Kharkow) a trouvé dans le sang la teneur élevée d'acides aromatiques, productions de la putréfaction, et le trouble de praticabilité de la barrière hémato-encéphalique, les changements dans le central système nerveux et dans la liqueur. KHOKHOL (Kiev) a prouvé que les toxicoses provoquent les changements dans la structure des capillaires.

Professeur SKVORTZOV (Moscou) a élaboré en détail l'anatomie pathologique de septicémie des enfants de bas âge (surtout l'anatomie pathologique d'ombilic). SPERANSKY, LANGOVOY et leurs collaborateurs ont donné au Congrès des pédiatres de l'Union, qui vient d'avoir lieu à Moscou, la caractéristique détaillée du syndrome toxico-septique et ont révélé la signification de carbo-anhydrase, la capacité phagocitaire des leucocytes, l'énergie complémentaire du sang comme indice de l'état immuno-biologique de l'organisme. KASANTZEVA a révélé le rôle du syndrome hémorragique; KRESTOVNIKOFF et STERN ont découvert le rôle de l'agent pathogène de susnommé syndrome et les moyens de lutter contre lui. KHOKHOL a prouvé la présence de considérables changements fonctionnels et morphologiques dans la région de la barrière hémato-parenchymateuse, liquéfaction de la substance argyrophile, liée avec l'augmentation de hydrophylie des tissus et la disposition aux oedèmes. DOMBROVSKAYA (Moscou) a démontré que du temps des états dystrophiques, les changements des fonctions du côté des organes respiratoires, de hémapoèse, de circulation du sang et de digestion de même que

l'abaissement des indices de l'immunité et du titre de complément. KRASNOGORSKY (Leningrad) a prouvé que la dystrophie abaisse l'excitabilité de la corticalité cérébrale, l'état de hypo-réflexité corticale et l'arrêt de développement des fonctions corticales surtout l'activité du second système de signaux.

Dans ma présente communication je voudrais vous mettre au courant de nos récents travaux dans le domaine des études de pathogénie des états toxiques, septiques et dystrophiques en les considérant séparément de même qu'au point de vue de leur connexité et leur influence réciproque. Nos observations menées conformément au plan établi d'avance par une grande collectivité de mes collaborateurs ne sont pas tout à fait achevées et je puis vous présenter seulement les résultats préliminaires. Pour approfondir l'étude de ces états il faut que nous les étudions séparément ne les réunissant pas dans un amas de syndrome toxico-septique ou septico-dystrophique.

Les états toxiques et septiques révèlent toujours l'affection de l'organisme en entier, la perversion des fonctions de tout un rang d'organes et de tissus, le trouble du système entier des mécanismes régulateurs.

Si nous voulons comprendre ces états, nous devons apprendre le plus complètement, le plus profondément, le mieux possible les propriétés et la réactivité du système physiologique de tissu lamineux, les appareils reticulo-endothéliales et hémopoétiques du système endocrino-végétatif, l'état des régulateurs neuro-humoraux, les barrières physiologiques de même que les fonctions de différents organes et tissus dans leur connexité mutuelle.

Qu'est-ce que c'est que l'état toxique à la lumière de nouvelles données et à la lumière de l'étude de la réactivité?

L'état toxique indique premièrement une profonde lésion des fonctions des organes et des tissus et un trouble profond de l'activité des mécanismes régulateurs. Au fond c'est la perversion de la fonction de la foie — ce premier régulateur du métabolisme et la barrière pour les substances toxiques, c'est à dire, c'est l'état qui peut être désigné comme hépatodysergie. La hépatodysergie peut se développer d'une manière brusque comme résultat de la pénétration dans la foie d'une grande quantité de matières toxiques d'une nature bactérienne ou alimentaire, ou graduellement, si ces matières, même en petite quantité, pénètrent lentement et atteignent l'organe dont la constitution est de moindre valeur, ou affaiblie déjà par les affections ou par la dystrophie. Très importants sont: le degré de la stabilité de l'enfant envers les variations de la balance d'eau, la hydro-labilité et l'imperfection de la régulation endocrino-végétative et nerveuse. La déhydratation apparaît comme un des moments fondamentaux qui produisent la perversion de la foie et sa transformation en un «laboratoire des toxiques». L'acidose qui se développe en même temps soutient plus encore le cercle vicieux et

augmente la catastrophe du métabolisme qui touche à tous les aspects de métabolisme: gazeux, hydro-minéral, carbohydrate, gras, albumineux, vitamineux, comme nous le témoignent les résultats des travaux de notre clinique de ces dernières années. Un rôle important dans les procès d'autorégulation joue le système des ferments et des catalyseurs du procès oxyréducteur. Du temps du toxicose, le système de fermentation du sang est fortement opprimé, surtout la force lipolitique du sang (3,5 au lieu de 8,3 d'après la norme). Le ferment de catalase en dépit de la condensation du sang se diminue en force conformément à la forme plus ou moins sévère de toxicose. Le ferment carboanhydrase se diminue en force quelque peu seulement. Le glutation donne en moyenne le chiffre proche de la norme mais la saturation par lui des érythrocytes est minimum. L'acide ascorbique — le régulateur puissant des procès d'oxyréduction pendant des états toxiques — se diminue considérablement dans le sang et tombe fréquemment jusqu'au zéro dans le liquide céphalorachidien cependant sa teneur dans les organes est la même que la norme. Il faut croire, que durant le toxicose dans le sang et dans la liqueur les conditions ne sont pas favorables, pour la manifestation de son activité. Au moment de détérioration de la barrière hématoencéphalique et de pénétration dans la liqueur des productions toxiques l'influence régulatrice du système central nerveux s'interrompt. Dans ces conditions l'état dystrophique est inévitable. En connexion avec la circulation des productions pathologiques de métabolisme la sensibilisation de l'organisme doit avoir lieu.

En résultat de perversion des fonctions des tissus reticuloendothelial et connectif, et d'abaissement de la force de résistance — l'état septique se développe facilement. Le développement de ces états témoignent que la barrière hémohisto-parenchymateuse ne peut pas remplir ses fonctions et laisse l'organisme sans moyens de défense. Dans la région de l'étude de pathogénie des états toxiques on a déjà beaucoup fait. Mais les moyens d'influencer le système des régulateurs sont encore étudiés insuffisamment.

Je passe à l'état septique. Seulement les formes fortement prononcées de septicémie donnent un tableau définitif pathologo-anatomique et permettent de désigner du vivant ou à la section l'agent pathogène défini. Sans doute il en existe beaucoup d'états qui ne peuvent pas être définis cliniquement autrement comme les procès latents ou masqués de septicémie bien qu'on ne réussisse pas de définir la porte d'entrée et de dégager du sang l'agent pathogène.

La septicémie est une affection pendant laquelle un foyer infectueux se forme quelque part dans l'organisme, d'où les microbes pénètrent de temps en temps dans le sang, provoquant chaque fois une réaction spéciale du côté de l'organisme. Cette réaction se manifeste par des symptômes cliniques originaux: le changement de sensibilisation, le trouble

des fonctions et de la réactivité de différents systèmes et, dans les cas graves, le développement de la régénération des organes parenchymateux. Le diagnostic de l'état septique peut être posé même sans dégagement de l'agent pathogène du sang, si l'on a la courbe caractéristique de température, le tableau du sang, l'écoulement prolongé de la maladie, l'apparition de taches en temps sur la peau de différentes espèces d'éruptions, les hémorragies aussi que les épreuves découvraient une montée de sensibilité de l'organisme (à l'exception, sans doute, des cas de tuberculose, brucellose, endocardite, cholepathies, dysentérie chronique, etc...). De même que la septicémie manifeste, l'état septique peut prendre des formes différentes et un écoulement régulier. Le caractère de la réaction dépend moins de l'agent pathogène, que de la réactivité de l'enfant.

Le diagnostic précoce de l'état septique doit commencer avec la dystrophie de l'enfant qui se développe à vue d'œil avec le changement du coloris de la peau en teint pale, couleur de cire avec une petite nuance jaunâtre, l'apparition des hémorragies même isolées ou des éruptions érythémateuses de la température intermittente, l'anémisation et la dysergie générale.

Au fond de l'état septique il gît, à ce qu'il paraît, l'autoblocage du système réticuloendothélial avec la répression de la capacité de formation des substances immunes et du phagocytose. Les expériences menées dans notre clinique ont révélé que la capacité absorbante (phagocytaire) de ce système chez les animaux jeunes est pire et se diffère de celle des animaux adultes.

L'absorption des couleurs et de l'encre de Chine chez eux se fait principalement dans la rate et dans la foie, tandis que la foie des animaux adultes n'absorbe pas les couleurs. L'accumulation des couleurs n'atteint son maximum que dans deux jours pleins et reste longtemps stable, ce qui prouve que l'absorption des couleurs ainsi que leur dégagement des cellules sont très lents.

À l'égard de microbes, les animaux jeunes possèdent la capacité bien prononcée de les bien retenir dans la foie et plus faiblement dans la rate et dans les poumons. Chez les animaux jeunes, les amas autour des microbes, des éléments cellulaires des cellules leucocytaires et lymphocytaires sont exposés plus faiblement que chez les animaux adultes. Si chez les enfants les cellules de réticuloendothélium phagocytent avec moins d'activité les microbes pénétrés dans l'organisme, les détruisent plus lentement, possèdent une capacité moins prononcée de limiter par la barrière cellulaire l'amas de microbes — on peut comprendre que cela donne aux microbes la possibilité de circuler dans le sang, se fixer dans de différents organes, se multiplier et donner à l'affection un caractère septique.

L'épreuve avec le bleu de trypan prouve que ces faits sont justes

aussi à l'égard des enfants. Le bleu de trypan pendant les états septiques donne les chiffres comparativement bas, témoignant l'absorption lente des substances qui teignent. L'endommagement de l'endothélium des capillaires est prouvé par nos observations capillaroscopiques: les capillaires acquèrent la forme parétique, sinueuse mince, réunie en touffes divergentes d'un tronc en éventail ou en candélabre. Quand la morphologie et la fonction des capillaires se pervertissent, la barrière hémohistio-parenchymateuse devient praticable pour les matières toxiques qui circulent simultanément avec les microbes dans la lymphe et dans le sang. Jusqu'à ce que l'état toxique n'est pas commencé et la balance d'eau n'est pas fortement troublée, les cellules des organes conservent leur structure en réagissant seulement par une dégénération peu prononcée. Du temps de la réaction hyperergique se développent les changements profonds dégénératifs des cellules. Quelquefois ces changements sont irréparables. Ces dernières années notre clinique travaille à l'éclaircissement du caractère des troubles du métabolisme, des fonctions des organes et des mécanismes régulateurs aux temps des états septiques. On a réussi à mettre en lumière un abaissement apparent de carboanhydrase avec l'abaissement de coefficient d'anhydrase (saturation d'érythrocytes). La glutination de sang est de même abaissée jusqu'aux 80 % de la norme avec la saturation basse d'érythrocytes. Dans tous les organes, surtout dans la glande supradrénale, on peut constater l'abaissement de la teneur d'acide ascorbique, ce que n'est pas indifférent à l'organisme.

L'appareil fermentescant du sang est modérément abaissé. La fonction relatrice du système endocrino-végétatif et central nerveux devient un peu pervertie. Le trouble du métabolisme n'atteint jamais le degré de celui que nous voyons durant les états toxiques.

Toute réduction de multiplication des microbes, l'abaissement de leur virulence, la limitation des foyers et le développement de l'immunité peut donner à l'écoulement de procès septique une forme lente ou l'atteindre tout à fait, mais à la nouvelle infection ou au développement de la dystrophie il peut s'enflammer de nouveau. Du temps de nouvelles explosions, grâce à l'épuisement de mesenchime et au blocage, les réactions d'immunité se développent dans un plus faible degré.

Les états septiques peuvent se différer d'après le tableau clinique ainsi que d'après leur origine.

La septicémie des nouveau-nés donne toujours l'écoulement plus pénible parceque les mécanismes réactifs fonctionnent defectueusement. La connaissance de pathogénie des états septiques et de ses particularités en dépendance de la porte d'entrée doit nous aider dans des questions de la prophylaxie et du traitement.

La lutte contre les états septiques doit être fondée non seulement sur les mesures de liquidation des agents pathogènes (préparation sulfo-

amide, penicillin) mais aussi sur des mesures de l'abaissement de sensibilité, la restauration du système des régulateurs, le renforcement de la résistance et la création d'un bon entourage. La lutte peut aboutir à bonne fin si elle est commencée de bonne heure quand la réactivité et la résistance de l'organisme sont encore conservées.

Pour avoir la possibilité de distinguer à temps l'état septique et la différence de cet état de l'état toxique je donne une table différence:

L'état toxique	L'état septique
1) Les changements catarrheux séro-hémorragiques de l'intestin. Infiltration grasseuse de foie.	Les changements dégénératifs et l'inflammation interstitielle des organes internes.
2) La perversion prononcée des fonctions des organes internes.	moyenne.
3) Métabolisme fortement troublé.	troublé moyen de métabolisme.
4) La balance d'eau fortement troublée.	troublée modérément.
5) L'abaissement brusque de poids.	graduel.
6) La peau de couleur d'un gris terne; cyanotique.	très pâle, ictérique.
7) Les hémorragies et les éruptions sont rares.	fréquentes.
8) Turgor fortement changé.	changé modérément.
9) La conscience fortement obscurcie.	changement modéré.
10) La teneur d'érythrocytes et de hémoglobine est normale ou élevée.	l'anémie prononcée.
11) Leucocytose moyenne.	leucocytose aigue quelquefois leucémie.
12) Neutrophylie moyenne.	prononcée, poussée jusqu'au myelocite.
13) Monocytes en norme ou augmentés.	abaissés. Aneosynophilie.
14) Les tons de cœur étouffés, disparition d'un ton.	étouffés, Arythmies.
15) La pression sanguine est abaissée.	ordinairement normale.
16) Dans l'urine les traces d'albumen, sucre.	Albumen, érythrocytes, cylindres.
17) L'index phagocytaire est abaissé.	quelquefois élevé.
18) Les capillaires deviennent vides, inégalement distribués, le courant de sang est relenti.	minces, sinueux, se divergent en éventail.
19) L'épreuve avec du bleu trypan est abaissée.	donne des variations.
20) La carboanhydrase un peu abaissée.	fortement abaissée.
21) Épreuve avec du lait est négative.	souvent positive.
22) Glutination de sang est peu changé.	Abaissé.
23) L'acide ascorbique de sang est abaissé, dans les organes — en norme.	Abaissé dans le sang et dans les organes.

24/ Les ferments de sang sont fortement abaissés.	modérément abaissés.
25/ La régulation nerveuse est perverse.	modérément perverse.
26/ La régulation endo-crino-végétative est troublée et perverse.	perverse en partie.
27/ Le trouble de la barrière de foie, hématoencéphalique, hémoparenchymateuse.	Le trouble partiel de la barrière de foie.

Passons à la pathogénie de l'état dystrophique.

Les dystrophies peuvent se développer non seulement sur le terrain d'irrégulière nutrition et de différentes maladies gastro-enteriques (visibles ou masquées) mais de même sur le terrain des troubles de l'activité de foie, de pancréas, de système endocrino-végétatif et central-nerveux, ainsi que sur le terrain des défauts de la surveillance et de l'éducation. En général la dystrophie endogène a une signification plus grande que nous ne croyions pas.

Entre les états toxiques et septiques et la dystrophie il existe une étroite connexion mutuelle et une influence réciproque. Toxicose et septicémie mènent à la dystrophie. La dystrophie crée dans l'organisme la dysergie et se transforme facilement en état toxique et septique en établissant ainsi un cercle vicieux.

Au temps des états dystrophiques on peut observer les troubles plus ou moins grands des fonctions: sécrétoire, motrice et resorbante de l'appareil gastro-enterique, qui porte quelquefois un caractère récidivant. Mais ce n'est pas la chose principale. Au fond de chaque dystrophie gît la perturbation de la balance albumineuse, graisseuse, carbohydrate, minérale, vitamineuse de même que la perturbation des mécanismes régulateurs.

Le degré de la dystrophie dépend du degré de trouble de métabolisme et des régulateurs.

Le régulateur principal de métabolisme — la foie est troublée dans ses fonctions assez profondément. Les investigations de notre clinique ont démontré que la charge de glycocole et d'ammonium acido-acétique au temps des états dystrophiques donne le retour lent des aminoacides vers les chiffres de départ et l'accroissement insuffisant de l'urée de l'urine. Les barrières entérique et hépatique sont quelque-peu affaiblies et ne remplissent qu'imparfaitement la fonction de ne pas admettre dans le sang les productions toxiques.

La barrière hémohisto parenchymateuse fonctionne à la borne de ses possibilités. La régulation endocrino végétative s'accomplit imparfaitement grâce à l'altération des organes endocrines (la glande thyroïde et la glande surrénale en particulier).

Le système des régulateurs des procès d'oxyréduction en essentiel

est conservé. On a trouvé dans le sang la présence d'un certain hypovitaminose C, mais dans les organes, il n'est pas en moindre quantité que pendant d'autres états. Le sang contient moins de vitamines A et B mais la quantité de carotène et d'acide pyruvique est proche à la norme. La teneur de glutation dans le sang est 85 % de normale avec un coefficient moyen de saturation. La carboanhydrase donne les chiffres à peu près normaux avec la saturation satisfaisante d'érythrocytes.

On voit d'après ces données que le système de désoxydation est conservé mais les conditions ne sont pas favorables à son travail. L'appareil fermentatif du sang n'a pas assez de force et s'épuise facilement — c'est pourquoi la régulation de métabolisme intermédiaire s'accomplit difficilement. La composition originale du sang et des épreuves de l'activité fonctionnelle de mésenchime témoignent la suprême instabilité de l'organisme et son peu de pouvoir pour la lutte contre les microbes. Le degré de perturbation de nutrition et la gravité de dystrophie jouent un rôle décisif dans l'affaire de résorption et retention des ingrédients nutritifs.

D'après nos investigations, la retension d'azote chez les dystrophies d'un état grave est à peu près 0.017 g pour un kilogramme de poids, où la balance d'azote est 3—5 %. Les dystrophies dont l'état est moins grave donnent la retention d'azote en 0.09 pour un kg de poids quand la balance = de 20—30 %. La balance de graisse chez les premiers est seulement 41 %, chez les autres 91 %; c'est à dire, elle ne se diffère que très peu de la norme. Impulsion qui mène à la meilleure assimilation de nourriture et à l'abaissement de dystrophie souvent ne dépend pas de l'élévation de caloricité ou le changement des éléments de la nourriture mais de la reconstruction du système des régulateurs et du changement de la réactivité. Quelle est la conclusion générale de tout ce que nous venons de dire? — L'étude minutieuse de chaque enfant malade, de ses particularités réactives, de l'état des mécanismes régulateurs peut seul nous aider à choisir les moyens rationaux de la lutte contre ces graves états sus-dénommés. Nous devons apprendre à utiliser rationnellement les propres réserves de l'organisme, créer les conditions favorables pour le travail des organes internes, influencer et stimuler le système des régulateurs.

Dans tout cela gît le futur progrès de la science.

Dr. F. F. Tisdall, Toronto, Canada (no manuscript received).

Prof. C. B. Choremis, Athens, Greece: *The Child's Nutrition in Greece.*

The Greek people has paid a heavy tribute to the war. And this, not only by the great number of victims on battle-fields, by slaughter and executions under four oppressors, who were rivalizing in ferocities, but also, by all the other huge privations they had to bear during the

occupation. Unfortunately, its duration was too extended and its consequences on our people's health — on our children's, particularly — deeply rooted.

Otherwise, poor and frugal, our people, even in prewar time, was never discerned by abundance in means of alimentation. Consequently, the effects of war were far more immediate and deep. From researches on health conditions of 75 000 children of the Athens-Piraeus area, made in 1944—45, it is, indeed, brought to light that undernourishment, privations, unhealthiness have left behind deep traces on the child's physical & physiological conformation.

The results of our researches may be summarized as follows:

I. The weight & length of the infant born during the occupation, according to observation of obstetricians, such as Drs. Maroudis & Antonopoulos, presented great dissimilarities with normal: weight is below by 100—300 g, and length by 0.5—1 cm. This decrease in the infant's weight & length levels is noticed for the first time and was previously considered a phenomenon never to be met. We know, of course, that differences from racial idiosyncrasy are almost annihilated on the new-born infant, in such way that the offspring of a Chinese does not essentially differ from that of a Swede. And, further, regardless of the foetus, nature, itself, expediently averts any external unfavourable condition affecting its evolution the foetus living as a parasite, fed at his mother's prejudice, with no concern for privations likely to occur to her. But, the supplies of the Greek mother, at that period, were quite meagre, so that even those rules which were prescribed by nature were not kept. In order of making this disclosure more apparent, we note that this phenomenon was never observed in Vienna's famine, during the last war. And, as you know, Vienna suffered far more than, so this shows to what extent the Greek people's hunger reached. This intensive and biologically unprecedented alteration of the infantile organism was checked as alimentary conditions improved, but, what the consequences will be for the generation coming from this period still remains unknown.

II. The difference in weight and height which appears in our child has nothing to do with racial differentiations, first, because under 10 years of age, no evident racial differences have yet developed between children of different races; and, second, because it is very intensely noticed, even in the comparison of type, with a prewar Greek child. This below standard level weight in connection with height, in the third 5-year period of childhood, will certainly become more obvious in its fourth period, 15—20 years of age, because growth ends by that time, and thus proves how deep an alteration our race underwent. Dr. Valaoras, as a consequence, predicts a dwarfish generation.

III. The specific and detailed analysis of the weight curve in comparison with height, resulting from the above investigations, shows

I. Table of Weight.

Age	Number	Average	Deviation	Error
B o y s				
0—6 months	1301	6.311	1.513	0.041
6—18 "	4048	9.726	2.381	0.037
2 years	2153	11.563	1.723	0.037
3 "	2200	13.616	1.881	0.040
4 "	2860	15.380	1.928	0.036
5 "	2796	16.864	2.092	0.039
6 "	2551	18.616	2.237	0.046
7 "	1505	18.760	3.027	0.091
8 "	585	21.776	3.109	0.128
9 "	733	23.599	3.317	0.122
10 "	880	25.523	3.406	0.114
11 "	961	27.633	3.714	0.119
12 "	968	30.086	4.139	0.133
13 "	679	31.834	4.662	0.178
14 "	379	34.807	5.435	0.279
G i r l s				
0—6 months	1296	5.864	1.389	0.038
6—18 "	3733	8.044	1.234	0.022
2 years	1980	11.096	1.682	0.037
3 "				
4 "	2663	14.950	2.005	0.038
5 "	2703	16.523	2.112	0.046
6 "	2555	18.107	2.316	0.045
7 "	1440	19.519	2.356	0.065
8 "	558	21.543	3.365	0.142
9 "	710	23.124	3.389	0.127
10 "	898	25.397	3.622	0.120
11 "	975	28.035	4.119	0.131
12 "	1002	30.966	4.731	0.149
13 "	630	33.258	5.585	0.222
14 "	199	35.130	5.716	0.405

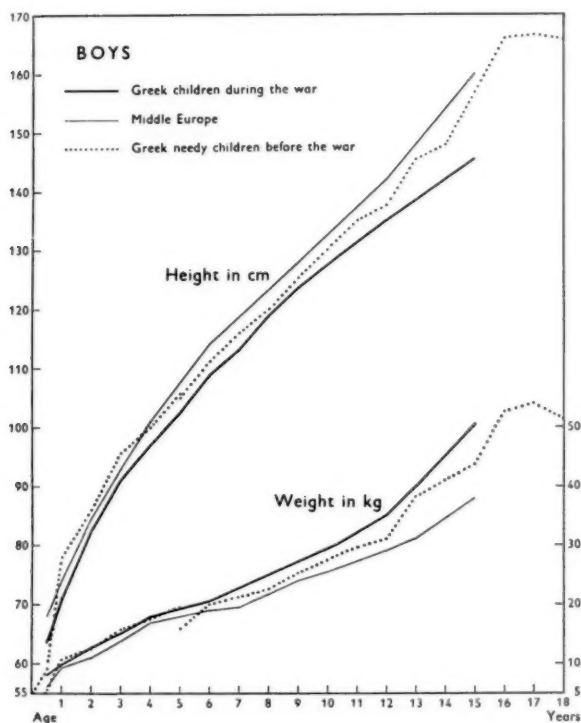
certain variations in respect with its course from the point of the physiological curve, which are of exceptional importance. And, first, the change appearing in the course of the curve, for boys and girls between 7—10 years old, corresponding to the abrupt increase of weight in this period preceding puberty (completion phase according Stratz) is not noticed in our curve, although it existed in the curve of the prewar child. The intensive growth in height of the girl, in her life period between 11—16 has also disappeared. As you are, certainly, aware, at this period the curves of the two sexes normally inter-cross and the female's curve crosses over and precedes the male's, then, gradually recedes back to its normal limits, between the 16th and 17th year, remaining under the

II. Table of Height.

Age	Number	Average	Deviation	Error
Boys				
0-6 months	1303	63.018	5.549	0.153
6-18 "	3949	71.253	5.414	0.086
2 years	1997	82.297	5.996	0.135
3 "	2194	90.702	5.377	0.014
4 "	2737	96.722	5.386	0.102
5 "	2788	102.427	5.561	0.105
6 "	2448	108.423	5.658	0.114
7 "	1335	112.349	5.395	0.147
8 "	585	118.917	5.451	0.225
9 "	728	123.899	6.091	0.225
10 "	88	127.255	5.680	0.190
11 "	992	131.541	6.149	0.200
12 "	978	135.358	6.506	0.208
13 "	672	138.642	6.968	0.268
14 "	376	143.031	8.991	0.420
Girls				
0-6 months				
6-18 "	1281	60.431	4.559	0.120
2 years	3710	69.924	4.910	0.080
3 "	1871	81.272	5.803	0.132
4 "	2006	89.517	5.355	0.119
5 "	2485	95.941	5.437	0.109
6 "	2697	102.085	5.558	0.107
7 "	2555	106.838	5.593	0.110
" "	1333	112.848	5.784	0.158
8 "	555	118.402	5.525	0.234
9 "	896	122.390	6.047	0.204
10 "	877	126.888	6.072	0.205
11 "	965	131.587	6.215	0.202
12 "	986	136.672	7.070	0.225
13 "	597	139.830	8.002	0.335
14 "	201	143.079	7.548	0.532

male's curve for her lifelong. This deficiency proves that such an important physical function as puberty was hindered in its morphological manifestations on the body, a fact which coincides with the gynecologists' observations that such a defective physical development goes in line with biological insufficiency of the organism. The frequent amenorrhea reported during the war by girls and the resulting under-functioning reflects their defective physical conformation in our days.

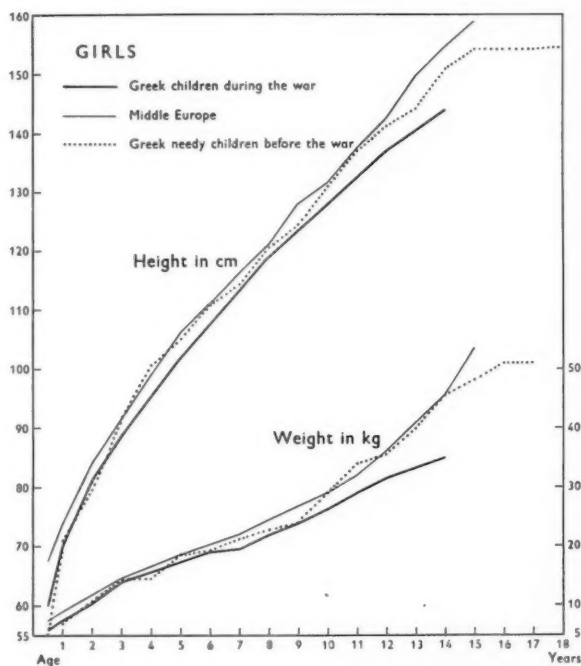
IV. The delay of development in weight and height, during the war, is neither uniform, nor identical all over the Athens-Piraeus region, but, in Piraeus and in the settlements of workers, more specially, it



appears to be greater than elsewhere. The resulting differences are shown in Table III.

V. Comparative research work by Dr. Valaoras, between the years 1942-44, on the function of growth shows that the growth in height of the Greek child does not manifest itself in time as it happens with weight, but later on. This is in absolute agreement with biological data, according to which man's stature as a more idiosyncratic function, i. e. depending from hereditary factors, in opposition to weight, is hardly ever affected by external influences, but, whenever this happens, as in the present circumstance, it discloses a deep organic injury.

By this fact, we feel it doubtful if not improbable, for children, belonging to this period, to ever acquire their normal structure, and, if ever they find themselves under favourable conditions, they will still remain, during their whole life, shorter than its previous generation.



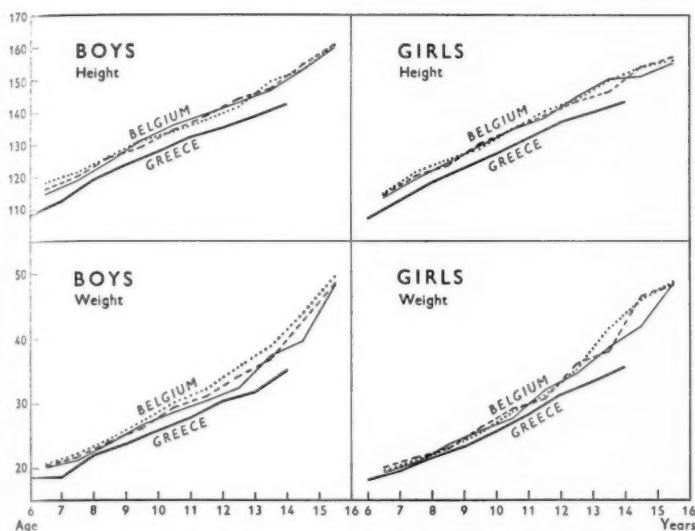
The significance of this fact is most important. The following designs and statements sketch out in detail all that has been exposed hereabove. In comparing these conclusions with similar ones from Belgium, where such researches have also been made (Rich. W. Ellis — Growth & health of Belgian Children. — Arch. of Disease of Children — Sept. 1945), although on a very limited scale, it is shown that the reduction in weight and height of the Greek child was far above the Belgian, since the curves of the Greek child are by 5—10 % below that of the most disfavoured amongst those who were under observation in Belgium. This difference by far surpasses the limits that racial differences trace between children of these two nations. It should further be interesting to note that the difference remained within these limits in the first year of the war only (1941—42), but, in the following years, it started being reduced, as the children were continually and gradually improving. The comparative curves which are shown (1944—45) in our Table emphasize the difference which resulted from our investigations.

TABLE III. Height and Weight of Belgian Pupils 1942—1943—1944.
(W. R. ELLIS.)

Age	Height (cm.)			Body Weight (kg.)		
	1942	1943	1944	1942	1943	1944
Males						
6-7	114.4	115.2	117.7	19.8	20.1	20.3
7-8	118.9	119.9	121.1	21.1	21.7	22.2
8-9	124.5	125.7	126.0	23.7	23.6	24.2
9-10	130.8	129.0	131.0	26.5	26.1	26.8
10-11	133.6	133.8	136.5	28.5	29.3	30.0
11-12	137.4	138.8	139.0	30.1	30.9	32.1
12-13	141.6	143.6	143.3	32.1	34.3	35.4
13-14	149.1	147.6	147.7	37.1	36.8	38.8
14-15	153.4	154.7	153.9	39.6	42.5	43.8
15-16	160.0	161.7	161.0	48.0	48.5	49.5
Females						
6-7	113.4	114.6	114.4	19.2	19.7	19.3
7-8	119.1	119.7	120.6	20.7	21.5	21.7
8-9	124.0	123.2	124.7	23.5	23.0	23.8
9-10	129.5	129.0	128.4	25.6	25.9	25.4
10-11	133.4	134.8	134.3	27.6	28.9	28.5
11-12	140.0	137.9	138.0	31.9	30.7	31.1
12-13	143.9	143.6	144.2	34.5	35.9	34.7
13-14	149.5	146.9	149.9	38.4	38.1	41.7
14-15	150.9	153.6	153.9	41.9	46.2	45.9
15-16	155.1	157.5	155.0	48.2	48.2	48.7

If one wishes to go deeper through an analysis of the above depressing conclusions ending these wide anthropometric researches on Athens-Piraeus region, he is bound to correlate these to the specific form of unhealthiness prevailing in Greece. Indeed, this unhealthiness reflects a deficient alimentation since long ago. The relation between the disease which always prevailed, in Greece, and their deep mutual dependence with alimentation is recognized by a long experience. Our child — or, at least, a very large percentage of our children — was even in prewar period quantitatively underfed. But, most of all, he was qualitatively underfed, also. His rationing in plastic substances is poor, i. e. in biologically higher albumens & fats. Our children need also milk, meat and butter. An average Greek, in prewar years, consumed only 39 litres of milk in average. — Hence, the terrible development of tuberculosis in large cities and of malaria in the country. This is how tuberculosis, which was always widely spread in Greece, assumed a pandemic character.

The number of positive tuberculin reaction with patients of my



Clinics, in general, were more than doubled in the period 1941—1945. — Attention should be particularly called on the increase of tuberculin reaction in infants between 0—12 months, who reached 35.6 % in 1946, that is, an increase we never found in Bibliography.

Also, statistics of the Greek Red Cross (Horocopos) prove that on 53 047 children who visited their dispensaries, from September 1, 1942—December 31, 1943, 19.1 % were attacked by tuberculosis, and 126 595 children examined from January 1, 1944—April 30, 1946, were tubercular, i. e. 51.3 %, which is approximately one half of the total number. These figures prove of the extent of tuberculosis in our Country, in the fact that on 191 deaths in the Pediatric Clinic of the National University of Athens, in 1946, 49 were due to tubercular meningitis. This brings to evidence the spread of tuberculosis by the chronic underfeeding of the Greek child, in wartime, which very nearly persists, even now after the war.

Our children's physical deficiency due to continuous undernourishment is also burdened by deeply traced marks of these eminently destructive diseases of which the Greek race always have suffered: malaria and tuberculosis. Unfortunately, we have not been able to control the development of malaria during the war because of lack of means to fight it, and moreover because the population following the war devastation of the country is homeless in great part and exposed to the malaria.

The continuous damage by tuberculosis & malaria on an essentially sensitive period of life such as childhood, creates through chronically a new type of child and adds a particular form and expression to our child's physiognomy which as endogeneous factor intermingles, hereafter, with our private idiosyncrasy. This form which now predominates in every pathological manifestation, affects the child's pathological reactions directly as well as indirectly. The general pathology of the Greek child and of the Greek adult is influenced by the anomaly of our racial idiosyncrasy and is dominated by diseases the development of which is favoured by this pathology, itself. It is a pathology of under and not over-nourishment. Our child's blood also discloses the unfavourable effect of the triple damage he underwent: underfeeding, tuberculosis, malaria. There would be no exaggeration in saying that we seldom see now in our Clinics, children with normal blood.

Peter V. Végheleyi (Pediatric Department of the Budapest University, Budapest, Hungary):

After the siege of Budapest, when there was practically no other food to be had than dry beans, we had ample opportunity to observe cases of nutritional edema. For a certain period too, there was no milk or any other source of suitable protein available, and therefore both the development and the course of the illness could be studied.

The very first organic change, at a time when there was still no variation in the level or ratio of the blood proteins and when hepatic function continued to be quite normal, was a diminution of the output of pancreatic enzymes, which was soon followed by an almost complete lack of these substances. The first to diminish and then to disappear was the lipase and the last the amylase. The concentration of both lipase and amylase in the blood was also considerably decreased. Then diarrhea sets in and the liver increases somewhat in size. Several tests, as that of Hanger, and the Takata one, become positive, but there was no shift in the Weltmann reaction as yet. This stage seems to last quite a considerable time. There were three infants who remained in this stage for more than four weeks. Their weight decreased or remained stable. There was anemia and a pronounced increase of reticulocytes and a progressive loss of albumen noted in one child but unfortunately no blood examinations could be made in the other two. If milk could be given at this stage, the condition improved at once. The pancreas began to secrete enzymes normally, the size and the functions of the liver became normal and the children continued to develop.

If, however, there was no protein available, edema set in after a time. The younger the infant the sooner edema appeared. Every kind of intercurrent disease, even the slightest cold, hastens its appearance.

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Most infants observed were already in this stage when admitted, showing all the classical signs of Mehlnárschaden. Enzymes were lacking in most of them, especially lipase. In most patients there was a shift to the right of the Weltmann band.

In those who died at this stage, the autopsy always revealed a severe fatty infiltration of the liver, closely resembling the picture found by Gillman and Gillman, and Waterlow. In later stages diffuse fibrosis was observed. The younger the infant and the longer the deficient feeding lasted, the more pronounced was the fibrosis. The final picture cannot be differentiated from portal cirrhosis or from that produced in rats fed on deficient diets by Himsworth and Glynn. Definite fibrosis of the pancreas was also present in all the cases in which the liver was cirrhotic.

It was tried to relieve the condition with different substances. The state could not be ameliorated by vitamin D, B₁, or nicotinic acid. 5 infants were given B₂ complex or riboflavin alone. This even seemed to aggravate their illness. The results with small amounts of milk were not at all satisfactory and it was felt that such feeding enhances deterioration.

Adequate amounts of milk, on the other hand, always brought relief in a few days. Pancreatic secretion became normal within three or four days; this was soon followed by a rise of the plasma albumen level and then the edema subsided. In fresh cases this occurred in about ten days while in neglected ones it took a much longer time. In the latter cases the tests of liver function gave pathological results for many a week afterwards. Three children of this group, who later died of other diseases months after they had been cured of nutritional edema, are the proof that the hepatic changes are irreversible, as pronounced scarring of the liver could be found in all three.

The secretion of enzymes seemed to be dependent of feeding with complete proteins, as the dysfunction of the pancreas ceased as soon as generous quantities of milk were given but returned if they had to be discontinued. It was much more difficult to cure these patients by parenteral administration of protein. At the time when no milk could be had, it was tried with two infants to check the condition by daily transfusions of blood and plasma. Neither showed a satisfactory response. One died in five days. The other remained unchanged for a week and then milk could be given. Next day the enzymes hitherto completely lacking appeared and the edema began to subside on the third day.

I do not wish to advance some theory which would reconcile all the facts presented above but the only conclusion which would seem possible to draw is that a diet deficient in adequate proteins inhibits the activity of the pancreas and that it is this dysfunction which may lead to those hepatic changes that are in the centre of the so called Mehlnárschaden.

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Dr. A. V. S. Sarma, Honorary Physician, Government Royafettah Hospital, Madras, India: *Malnutrition in Relation to Cirrhosis of Liver in Infancy and Childhood.*

A hypothesis is offered to explain the causation of hepatic cirrhosis in children. An allergic diathesis in the patient is probably the basis, ingestants being important. Excess of fat in cow's milk; insufficiency in the diet (especially in quality proteins and vitamins C, and factors of B complex); a toxic factor from the bowel; an infection (virus?) act singly or in unison and ultimately result in cirrhosis of liver.

A portion of the left lobe of the liver removed from a case of malnutrition under my care in Government Stanley Hospital, Madras, was studied. Clinical data on the case are these: A female child, five years old, from poor class, Hindu, Non-Brahmin. Admitted for swelling of the abdomen and feet of two months' duration. Had whooping cough two months prior to the swelling. Xerotic conjunctivae, dry pellagrous skin, and angular stomatitis present. Ascites and prominent abdominal veins present. Liver one half inch below costal margin. Spleen palpable. Lungs: a few basal râles heard. No sugar or albumin in urine. Blood serum: van den Bergh direct and biphasic positive. Mother's blood Wassermann negative. Post mortem, the liver was hard, bile-stained, and finely nodular. Under the microscope the liver showed fatty degeneration involving all the zones and almost all the cells. Slight increase in periportal connective tissue with lymphocytic infiltration present. These findings support Himsworth and Glynn.

Cases arising mainly from dietetic errors probably result in portal cirrhosis, and those wherein toxic elements predominate exhibit biliary cirrhosis. That such clinical types exist is my clinical conviction.

Reference:

The «Antiseptic», January—April 1946.

Plenary Session — Diseases Caused by Filterable Viruses.

REGATOR, Neurotropic Viruses.

Virus Infections of the Human Nervous System.

By **Albert B. Sabin, M. D.**

From The Children's Hospital Research Foundation, Department of Pediatrics
University of Cincinnati College of Medicine.

In this communication, I have chosen to survey some of the advances in our knowledge of the virus infections of the human nervous system during the past 10 years. During this period we have added to our information about diseases and viruses which were known before, we have separated as distinct entities diseases which must have existed before but had gone unrecognized, and we have discovered new neurotropic viruses for which, strange as it may seem, diseases still have to be found. To permit some sort of systematic approach, I have divided the known virus infections of the human nervous system into those which have their basic reservoir in human beings and are, therefore, world-wide in distribution, and those whose basic reservoir is extra-human in arthropods or lower animals and, therefore, in certain instances present only in certain parts of the world. In separate categories are a) the diseases for which a virus etiology is suggested by their pathology but the viruses are still unknown or poorly understood, b) the viruses which are known but the diseases they cause in human beings are as yet unknown and c) those diseases of the nervous system which are sometimes grouped with the virus infections but which may very well have another etiology. (Table I.)

TABLE I. VIRUS INFECTIONS OF THE HUMAN NERVOUS SYSTEM.
Classification Based on Information Available in 1947.

A. DISEASES AND VIRUSES KNOWN.

I. Basic Reservoir in Human Beings — Worldwide in Distribution.

1. Sporadic and Epidemic — Poliomyelitis.
2. Sporadic — Mumps (parotitis).
Herpes simplex.
Lymphogranuloma Venereum.

II. Basic Reservoir Extra-human.

1. Arthropod-borne Encephalitides.

St. Louis.	Rabies.
Western Equine.	Lymphocytic Choriomeningitis.
Eastern Equine.	(Pseudolymphocytic Choriomeningitis?)
Venezuelan Equine.	B Virus (MONKEY).
Japanese B.	
Russian tick-borne —	
(Louping Ill?).	
2. Transmitted by Animal Secretions or Excreta.

B. VIRUS ETIOLOGY POSSIBLE BUT VIRUSES LITTLE KNOWN OR UNKNOWN.

- Von Economo's Encephalitis Lethargica.
Herpes Zoster.
Australian «X» (May have been Japanese B).

C. NEUROTROPIC VIRUSES KNOWN BUT DISEASES OF HUMAN NERVOUS SYSTEM UNKNOWN.

- Viruses discovered in Africa — West Nile, Semliki Forest, Bwamba Fever.
- | | | | |
|---|---|---|---|
| » | » | » | So. America — Ilheus, Colombia «Mosquito» Viruses. |
| » | » | » | No. America — California «Mosquito» Viruses (Hammon). |

D. DISEASES SOMETIMES GROUPED WITH VIRUS INFECTIONS WITHOUT ADEQUATE EVIDENCE.

- Infectious Polyneuritis (Guillain-Barré Syndrome).
Postinfection and Postvaccination (Demyelinating) Encephalitis — measles, varicella, rubella, vaccinia, variola, mumps, «influenza», etc.
Acute Hemorrhagic Encephalitis.

Poliomyelitis, being the most important of the infections whose basic reservoir is in human beings, has received very intensive study during the past 10 years, but progress has been slow. The lack of a small, cheap, readily available experimental animal for work on poliomyelitis, probably more than any other single factor, has been responsible for the difficulties encountered in establishing the smallest fact and in the collection of all the information necessary for the full understanding of the natural history of the disease. For this reason Armstrong's demonstration in 1939 that a strain of human poliomyelitis virus could be adapted

through the monkey and cotton rat to the mouse constituted a very important step forward. Thus far, however, this discovery has failed to fulfill the original expectations, first because it has been possible to adapt only a few of the strains of virus to mice, secondly because the mouse-adapted viruses do not produce in mice or monkeys an experimental disease comparable to that in human beings, and thirdly because mice cannot, as yet, be substituted for monkeys in the search for poliomyelitis virus in human beings and their environment. By the end of 1937, the extensive studies of the behavior of poliomyelitis virus in rhesus monkeys so influenced the concept of its behavior in human beings that it was almost generally believed that the whole cycle of events consisted essentially of virus, which had its origin in the nose of one person, entering the nose of another and invading the nervous system by the olfactory pathway. Since experimental methods were discovered of chemically blockading this pathway, it will be recalled that extensive human trials were carried out during epidemics which proved to be without effect in preventing the human disease. However, the studies on rhesus monkeys also showed that it was possible to determine whether or not invasion by the olfactory pathway actually occurred, and when these methods were applied to the study of the human disease it became apparent not only that the concept of invasion by the olfactory pathway was untenable for human beings but also that the nasal mucosa was not the source of virus for human infection that it was believed to be. It soon became apparent that the occasional recovery of virus from human nasopharyngeal secretions was due to the presence of virus in the posterior pharyngeal wall rather than the nasal mucosa, and the improved methods for the detection of virus in the feces resulted in a tremendous amount of work which not only established it as a very rich and common source of virus in human beings, but also proved, what was only surmised before, namely, the importance of the large numbers of the slightly ill and apparently well individuals as sources and potential disseminators of the virus. The corollary studies on fatal human cases established that the source of this virus in the stools was the alimentary tract itself and not secretions coming

from the lungs or nose such as may account for the presence of tubercle bacilli or certain other bacteria in the stools; virus was recovered from the washed tissues of the tongue, oropharynx, duodenum, jejunum, ileum and colon. Since the virus in the stools has been found in at least 70 per cent of patients during the first two weeks after onset, in 50 per cent 3 and 4 weeks after onset, and in 27 per cent even as late as 5 to 6 weeks after onset, it would appear that it can continue to be liberated from the walls of the alimentary tract for a long time. However, there is still no direct evidence on how the virus reaches the alimentary tract and in which of its components it multiplies, if it multiplies there at all. The studies on the centrifugal spread of poliomyelitis virus away from the human central nervous system do not support the concept that the virus in the alimentary tract has its origin in the central nervous system or its ganglia. Although no definite lesions have been found in the nerve cells of Meissner's and Auerbach's plexuses in the gut, it does not mean that the virus may not multiply in them since virus studies on the entire alimentary tract in fatal human cases indicated that the localization of virus can be very spotty. However, the possibility has not yet been excluded that the virus, as it occurs in human beings, may multiply in the non-nervous elements in the tissues of the alimentary tract. The very fact that we can raise questions such as these indicates how incomplete our information still is.

Prior to 1937 it was generally doubted that poliomyelitis can result from feeding of the virus and the few positive results, which were reported by some and could not be repeated by others, were generally attributed to contamination of the olfactory area with the virus. However, experiments in chimpanzees and cynomolgus monkeys with viruses of recent human origin have established that the disease can be produced by feeding of the virus without invasion of the olfactory pathway, and the failures resulting from the use of virulent strains of virus, which had been passaged in monkeys for a long time, emphasized the special properties possessed by the virus as it occurs in human beings. The demonstration in 1941, that the so-called «filth» flies trapped in rural as well as urban areas during epidemics of poliomyelitis

were carriers of the virus brought up still another potential mode for the dissemination of the infection. The further proof provided in 1944 that food contaminated by such flies could produce infection in chimpanzees, indicated that this mode of virus dissemination might play a hitherto unsuspected role in the epidemiology of the disease, particularly since no other explanation was as yet available for the special prevalence of the disease during the summer and early autumn months and its very low incidence during the remainder of the year.

The other viruses of human origin, which are now known to produce infection of the nervous system, are mumps (epidemic parotitis), herpes simplex and lymphogranuloma venereum. Although the occurrence of mumps meningitis has been suspected on clinical grounds for many years, the recent development of complement-fixation and hemagglutination methods for the specific diagnosis of infection with this virus has provided definite proof of the etiological relationship of the mumps virus in a surprising number of cases of aseptic meningitis without parotitis. During the past 10 years, together with the proof of the etiological relationship of the virus of herpes simplex in such conditions as acute gingivo-stomatitis and Kaposi's varicelliform dermatitis, there has come the first satisfactory evidence that this virus occasionally goes beyond the skin and mucous membranes to invade the human nervous system, as it so frequently does in experimental animals. Since 1941, there have been reported 4 fatal cases of encephalitis due to this virus, one in a 4-week old child and the other three in American soldiers. Clinically, the manifestations were those of any other acute encephalitis and interestingly enough in no instance was there a record of obvious herpetic lesions on the skin or mucous membranes. The total duration of the illness was 6 to 13 days; diffuse encephalitic lesions with acidophilic intranuclear inclusions of the herpetic type were found post-mortem and the virus of herpes simplex was recovered in each case by inoculation of brain tissue in mice. In another case reported in 1943, the virus was recovered from the spinal fluid of a 15-year old boy in whom the clinical diagnosis was lymphocytic meningitis; this patient recovered

after an illness of 5 days and the etiological relationship of the herpes virus to the disease was indicated by the development of neutralizing antibodies during convalescence.

Satisfactory evidence that the virus of lymphogranuloma venereum can give rise to severe meningoencephalitis in man was brought forth in 1942. Among the unusual features were the cerebrospinal fluid sugar, as low as 17 to 20 mg. per cent during the acute state, a high pleocytosis and cerebrospinal fluid protein as high as 1 400 mg. per cent persisting for several months, and almost negligible, general, clinical signs of lymphogranuloma venereum, although the virus was recovered from insignificant lesions on the penis, from a slightly enlarged inguinal lymph node, and twice from the cerebrospinal fluid, the last time being 36 days after onset.

The greatest advance in this field during the past 10 years was made in our knowledge of the group of encephalitides which occur during the warm months of the year. The St. Louis, Western Equine, Eastern Equine, and Japanese B types of encephalitis occur in the summer and early autumn at a time when the mosquito vectors now known to carry the infection to human beings are most prevalent, while the Russian Spring-summer encephalitis, which is transmitted to man by the tick, *Ixodes persulcatus*, occurs in the spring and early summer when these vectors are most prevalent in the forests of the Far Eastern regions of the U. S. S. R. The Venezuelan virus first recovered in 1938 from cases of equine encephalomyelitis in Venezuela, and now known to be present in Colombia, Ecuador, Panama and Trinidad, has not yet been identified as the cause of an epidemic in human beings. However, human laboratory infections have occurred, and the virus has been recovered from a U. S. Navy seaman who died after acquiring the disease spontaneously in Trinidad in August, 1943. The mosquito, *Mansonia titillans* Walker has been found naturally infected and capable of transmitting the Venezuelan virus. The work of the past 10 years has shown that basically the epidemiology of the so-called equine virus encephalitides and the Japanese B and St. Louis types

were similar in that many vertebrate hosts, in addition to human beings and horses, were affected by these viruses in nature, and that mosquitoes which were found to be naturally infected were the epidemic vectors. Fortunately, the infection produced by these viruses is silent or inapparent in the vast majority of vertebrates, including human beings. Nevertheless, there are occasions when epidemics affecting thousands of human beings appear in the most unpredictable manner. In the spring-summer encephalitis of the Far East the naturally-infected tick fulfills the criteria for a true reservoir in that the virus is transmitted through the ova from generation to generation. In the group of summer-autumn encephalitides, however, the real reservoirs are still unknown, because thus far there is no satisfactory evidence that either the vertebrates or the mosquitoes serve as anything but temporary hosts for these viruses. The recent demonstration that the chicken-mite, *Dermanyssus gallinae*, can constitute a true reservoir for the viruses of St. Louis and Western Equine encephalitis in certain parts of the U. S. A. is an important advance. While there is already evidence that this does not obtain for the same viruses in other parts of the U. S. A. or for Japanese B encephalitis in Japan, it points to the existence of a dual mode of dissemination of these viruses in nature. Thus, there would appear to be one mechanism or cycle by which these viruses may be maintained from year to year, winter and summer, and another involving transmission to man and certain other vertebrates by means of the infected mosquitoes. In the case of Japanese B encephalitis, for example, evidence has recently been obtained which suggests that during nonepidemic years in endemic areas, the virus can be widely disseminated among horses, goats, pigs, cows, etc. at a time when human beings and chickens are affected little or not at all.

In the group of viruses transmitted to human beings through the agency of animal secretions and excreta, there is good reason for including the virus of lymphocytic choriomeningitis. Ten years ago, shortly after the virus was first discovered, it was believed, or hoped, that it might account for the major portion of

the cases of aseptic or lymphocytic meningitis of unknown etiology. However, the experience of several laboratories in the U. S. A. has now indicated that this virus probably accounts for less than 10 per cent of the cases of aseptic meningitis. Mice, dogs and perhaps other animals may be the source of virus for human infection. The virus of pseudolymphocytic choriomeningitis was reported from England in 1939 as having been recovered from two human beings, one with meningitis and the other with mild encephalitis, but there have been no other reports concerning it since then. This virus is immunologically distinct from that of lymphocytic choriomeningitis and also has a larger particle size. The bulk of the cases of aseptic meningitis still remain without an etiological diagnosis even when tests for the mumps virus are carried out, and there is evidence to suggest that the virus of poliomyelitis may be responsible for many of them in the winter as well as in the summer.

Time will not permit a discussion of the other viruses listed in the table, except for a few words about the new neurotropic viruses discovered in the past 10 years whose relationship to disease of the human nervous system is not yet apparent. In Africa, the West Nile and Bwamba fever viruses were recovered from the blood of natives with mild febrile illnesses by mouse inoculation, while the Semliki Forest, Ilheus, the Colombia and California «mosquito» viruses were all picked up, also by mouse inoculation, during the routine search for known viruses among mosquitoes in Africa, South America and California. While there is no evidence now that these viruses can cause anything but mild or inapparent infections in man, it should be remembered that that would also have been the status of the Western Equine virus 20 years ago if by chance it had then been similarly recovered from *Culex tarsalis* mosquitoes. For, although the Western Equine virus was first recovered from horses in 1930, it was not until 1941 that the first epidemic of encephalitis affecting over 3 000 people was recognized as being caused by this virus. It is, therefore, important to be aware of the existence and potential menace of these new viruses.

Discussion.

Dr. **Leslie Alm**, *Neurotropic Virus Infections in Gothenburg*. (From the Bacteriological Laboratory, Gothenburg. Chief: A. WASSÉN, M. D.)

In Sweden, but specially in Gothenburg, a town with a population of 325 000 people, has since many years encephalomeningitis been observed which clinical obviously do not belong to either Economos or Heine-Medins diseases.

The first clinical description of this nervous disease was made by Dr. A. Wallgren who in 1924 gave a paper where he described several cases under the name of «Acute aseptic meningitis».

Personally, I have seen several epidemics, which usually are small and circumscribed concerning encephalomeningitis among soldiers, nurses and children. But as a matter of fact, most cases appear sporadic.

In Gothenburg we see each year about a 100 cases of encephalomeningitis (but 1945 we had a peak with 190 cases). The mortality is about 10—12 %. Most cases appear during the winter. Very many, on an average 50 %, have a previous story of overrespiratory infection. The clinical picture is various as in all cases of encephalitis caused by so-called neurotropic viruses. The common types are in regard to their severity following:

- 1) Common cold group
- 2) Oculo-vestibular group
- 3) Meningitis group
- 4) Hemiplegic or palsy group. In this last group, most of the fatal cases appear.

The virus investigation concerning the cause of the meningoencephalitis started 1946, some previous work was done 1945. The way this investigation is carried out and the results hitherto are shortly following.

Practically all hospitals in Gothenburg lay on the same place with the bacteriological and virus laboratories in the center. On all cases of acute encephalomeningitis, the spinal fluid is drawn immediately and about a half an hour later, injected in the brain of the 10—3 weeks old Swiss mice and in some cases also on the membrane of 13 day old eggs. On all patients who die, autopsy is performed as soon as possible, 2—12 hours post mortem. By this way, we receive fresh material. Blood samples are drawn as soon as the patient arrives at the hospital and then every 10 days.

Up-to-date, 650 spinal fluids have been injected. We have caught one herpes strain from a man 50 years old, ship-builder, who was brought to the hospital on account of a severe meningitis. Of ten mice injected, 7 came down. The patient also showed a positive complement fixation against herpes.

About 25 brains have been investigated. From two brains, pleuropneumonia-like organism have been recovered, several times from the same brain. The strain caused rolling disease among the injected mice. A nurse working with this strain, came down in clinical mild infection with slight nervous disturbances. Blood drawn from her revealed the same organism. We used in this case eggs for primary isolation. At least 5 times we have made 8-10 blind passages with mouse brain, but have failed to establish any spontaneous pleuro-pneumonia organism. What this means, that we have been able to recover pleuro-pneumonia-like organism from the brain of patients, I do not know.

The complement fixation has been carried out against herpes virus, using mouse brains and egg membranes as antigens — each sera at the same time, also runs against — a normal mouse brain and egg membrane as control. The fixation test has also been carried out against L. C. M. virus using guinea pig spleen as antigens and normal spleens as control. It can be stated immediately that 506 sera tested against L. C. M., so far have been negative. Against Herpes, 843 sera from 300 patients suffering of encephalomyelitis have been investigated. Of these 24 gave a positive fixation, which appears two weeks after the onset of the illness and disappears after 4 weeks. These 24 sera also neutralized the virus. During the same time also 300 negative Wassermann sera have served as control, in no instance has any positive fixation appeared, but 2 suspect positive should be mentioned. Cases suffering of herpes labialis, stomatitis, herpes facialis, keratitis herpetica, have all failed to fix the complement.

Our impression now is that positive fixation with herpes is only possible when you are dealing with a systematic herpes infection. It should also be mentioned that the fixation is of very short duration, but as far as our group is aware, it is significant when it appears.

It is also our impression that about 20-25 % of aseptic encephalomyelitis are probably due to herpes virus. The rest 75 % we do not know the cause of.

Dr. Harold K. Faber, Department of Pediatrics, Stanford University School of Medicine, San Francisco, Cal., U. S. A.

Dr. Sabin's able review has placed before us some of the puzzles that remain to be solved in that much-studied disease, poliomyelitis. Since my own special interest has been directed mainly to two of them, namely the ingress and egress of the virus in the body, my comments will deal with these.

As Dr. Sabin has pointed out and is now generally accepted, primary infection in man does not follow the olfactory route, which has been ruled out by the absence of lesions along its peripheral pathways. There is, however, human pathological evidence that in some other peripheral

nerve pathways connecting with mucous membranes, notably those of the fifth cranial nerve, lesions are present in abundance: which is, therefore, consistent with, though admittedly not final proof of, entry along such channels. Unfortunately, human material can never be obtained until the disease has run its course and the primary pathways of entry are apt to be obscured by widespread dissemination of virus and lesions. We are therefore obliged to turn to experiment for solution of the problem, always keeping in mind the necessity of so planning experiments that they will be consonant with the probable conditions of human infection — a precaution which we failed to observe in the case of the olfactory route.

The general principle of centripetal spread of infection from peripheral nerve exposure to the peripheral ganglia and thence the central nervous system has been clearly demonstrated in animals. Feeding experiments have been of particular interest regarding the portal of entry since we have reason to suppose that virus often or usually first enters the body through the mouth in one way or another.

Using recently isolated human strains of virus, Dr. Sabin has found and we have confirmed, that 40–50 % of cynomolgus monkeys given virus in their food develop clinical poliomyelitis. In such experiments, the entire alimentary tract is, of course, exposed, and it is difficult to say whether infection entered at the upper, oropharyngeal level or the lower, gastrointestinal level. To answer this question we devised a method of inserting virus-filled capsules into the esophagus, thus confining exposure — barring accidents — to the lower, gastrointestinal level. With Dr. Sabin's Per strain, none of 26 monkeys developed poliomyelitis, and with our Cam strain only one of 18 came down. These were the same strains used in simple feeding and in comparable amounts. A careful histological survey of the single animal succumbing to the disease gave rather strong evidence that primary infection had occurred in the oropharynx through the fifth cranial nerve, rather than through the gut and it seemed likely that in this case virus had accidentally been regurgitated or else had been accidentally ingested from the animal's own stools. In any case, it is clear that primary intestinal entry after virus feeding, if it occurs at all, is a very unusual event in the cynomolgus monkey, and our human histopathological data tend to support the same view for man. I am therefore inclined to believe that poliomyelitis is not primarily a gastrointestinal infection but rather an oropharyngeal one.

While the mechanism by which poliomyelitis virus appears in the pharynx and intestine remains obscure in certain respects, I personally question whether we need to consider too seriously the occurrence of virus multiplication in non-nervous tissues such as intestinal epithelium until we have exhausted the possibilities based on neurotropism. I hold a strong conviction that the virus has no host other than the nerve

cell, and I feel that excretion from infected peripheral nerve tissue by a mechanism that I have suggested elsewhere remains the most probable explanation. Melnick's experiments, for example, in which virus appeared in the stools after parenteral inoculation are hardly susceptible of any other interpretation. In our own capsule feeding study the intestinal mucosa was heavily exposed to virus in all 44 animals, yet the only instance in which virus continued in the stools after the immediate post-feeding period was the animal that developed poliomyelitis.

To study this problem of excretion along nerve channels, we have briefly exposed the central end of a cut branch of the fifth nerve in the cheek and looked for virus in the nasopharyngeal secretions and stools on the succeeding days. On the second day, no virus was found in the secretions; on the third day, it was present in the secretions but not in the stools; on the fourth day it was present in both, and also in the homolateral but not the contralateral Gasserian ganglion. Thus, at a very early stage of infection virus moved centrifugally as well as centripetally, and was excreted on the pharyngeal surface. Appearance of virus in the stools probably resulted from swallowing. Such experiments may well have a direct bearing on excretion in human poliomyelitis since the Gasserian ganglia have been shown by us to contain heavy lesions in about 75 % of human cases, and other ganglia connected with the oropharynx somewhat less often, all of which could readily serve as sources of virus in the pharyngeal secretions. I lack time to pursue the implications of this thesis, many of which remain to be explored, but I venture to hope that some further progress has been made toward an understanding of the problems of entry and exit of poliomyelitis virus into and out of the body.

RELATOR, Respiratory Viruses.

Respiratory Viruses.

By **Thomas Francis, Jr.,**

Professor and Chairman, Department of Epidemiology School of Public Health, University of Michigan, Ann Arbor, Michigan.

Continued studies of the viruses causing respiratory disease have succeeded in giving a clearer picture of the clinical and epidemiologic aspects of influenza. Moreover, the extended studies of the past five years have indicated that vaccination against influenza A and influenza B can be achieved. There remain,

however, problems of the significance of strain variations and the time through which effect can be obtained.

Little added information concerning the common cold has been obtained.

Atypical pneumonia has been studied by many investigators without conclusive data as to etiologic agent or prevention. Eaton and his associates have presented data which they interpret to mean that a causative virus has been isolated and maintained in chick embryos. Their serological studies must be considered in relation to the cold hemagglutinins, agglutinins for non-hemolytic streptococci, and non-specific complement-fixing antibodies which are encountered in the disease.

The Commission on Acute Respiratory Disease was able to transmit atypical pneumonia to human subjects and to demonstrate that two different clinical pictures were separable by this procedure.

Still other information of the psittacosis-lymphogranuloma venereum group of viruses has demonstrated that these agents may be related to respiratory disease in various species of animals and suggest that a carrier virus may occur in man.

Mention can also be made of other viruses which may induce respiratory disease in man.

Discussion.

Dr. **John M. Adams**, Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota, U. S. A.: *Primary pneumonitis in infancy.*

This condition is a highly contagious, epidemic disease involving premature and young infants. The clinical signs are sneezing, cough, dyspnea and cyanosis. The physical findings and fever are minimal, the roentgenograms revealing soft infiltrative shadows, most frequently in the right upper lobe with associated atelectosis and emphysema. The pathological picture is distinctive, being primarily bronchiolitis, with proliferation and destruction of lining epithelium and peribronchial mononuclear infiltration. The involved epithelial cells contain specific cytoplasmic inclusion bodies. Pharyngeal tissues in these same patients contain many inclusion bodies of a similar character.

The prematurely born infant is highly susceptible to this disease and the mortality has been approximately 85 percent in these patients.

No specific therapy has been found, the continuous administration of oxygen is the main recourse.

Preliminary biological studies have ruled out influenza A and B, but have not as yet identified the agent, although respiratory disease with inclusions has been produced in newborn calves. Egg embryo studies are now in progress, as well as further animal studies.

Prof. Charles A. Janeway, Children's Hospital, Boston, Mass., U. S. A.

In at least two viral diseases, influenza and measles, pathogenic bacteria in the nasopharynx are very prone to invade other portions of the respiratory tract — paranasal sinuses, middle ear, and bronchi. Much of the serious sequelae and mortality from these two important diseases can be prevented by control of secondary infections, either by a chemotherapeutic attack on the bacteria or a biological attack on the virus.

The ability of the sulfonamides and penicillin to control bacterial invasion of the lung, even after it has begun, has been clearly proved; and they should be even more effective in preventing such invasion.

Dr. Francis has described the development of a biological approach to prevention of influenza A and B by immunization with vaccine. As pediatricians we must determine the extent to which this vaccine should be used in childhood, when influenza is relatively mild and now that bacterial complications can be treated with chemical agents.

Efforts to develop a measles vaccine by Stokes, Rake, and their associates have not yet succeeded, and we must still use sera for attenuation or prevention by passive immunization. Convalescent serum is effective, but is difficult to obtain and may transmit serum hepatitis from donor to recipient. During the war, human blood, collected by the American Red Cross, was fractionated on a large scale, yielding an antibody fraction (gamma or immune serum globulin) in which antibodies are concentrated 25 times over the initial pool of plasma. Prepared from the blood of from two thousand to ten thousand donors, gamma globulin has proved to be uniform in potency, safe for intramuscular injection, and does not produce hepatitis. Dr. Stokes and his associates proved its value for the prophylaxis of measles, and its widespread use has established the following points:

1. When gamma globulin is injected into a child who has been exposed to measles, the outcome depends more upon the dose than upon the interval between exposure and injection.
2. A dose of 0.2 cc per kilogram of body weight will prevent measles in at least 80 per cent of exposed children.
3. A dose of 0.04—0.05 cc per kilogram will prevent measles in very few children but will lead to a mild attack in about 70 per cent.

4. This type of mild measles is seldom followed by bacterial complications.

5. It is possible to stop measles epidemics in hospital wards without closing them, by administration of gamma globulin to exposed children.

Thus, two methods — chemotherapy against the bacteria, and immunization against the virus — have become practical means to lower the mortality and lessen the serious pulmonary and other septic complications of influenza and measles.

Plenary Session—Chemotherapy of Infectious Diseases.

RELATOR.

Chemotherapy of Infectious Diseases.

By **Chester S. Keefer.**

Evans Memorial Hospital, Boston.

In the time allotted to me, I propose to say something about the diseases in which streptomycin is effective and to discuss briefly the various side effects of the drug. It can be said that streptomycin has taken its place along with the sulfonamides and penicillin as a valuable chemotherapeutic agent in the treatment of a number of infections. In a study of 2 950 cases that have been reported to us, the following facts stand out.

It is the best agent available for the treatment of tularemia, when 0.5 to 1 gram a day is given for 5 to 7 days. The fatality rate in the pneumonic form is reduced and in the ulceroglandular form the effect on the local lesion and constitutional symptoms is very striking indeed. The total duration of the disease is reduced and suppuration is often aborted.

In urinary tract infections, between 65 and 70 per cent of patients are improved when 1 to 2 grams are given daily for 5 to 7 days. Failures are usually due to the presence or appearance of resistant strains of bacteria, the presence of an obstruction, a foreign body such as a stone or catheter, an undrained abscess or a granulating wound. The urine should be made alkaline in all cases during treatment.

In *H. influenzae* meningitis or in meningitis due to other gram negative bacilli, the fatality rate has been reduced. Eighty per cent of all cases of *H. influenzae* meningitis have recovered,

whereas 65 per cent of patients with other forms of gram negative bacillary meningitis have responded favorably. The results in tuberculous meningitis are not favorable, since only a very few patients have recovered and remained well.

In patients with bacteremia due to gram negative bacilli such as the colon bacillus, *Aerobacter aerogenes*, Friedländer's bacillus, proteus bacillus, and *B. pyocyaneus*, 65 per cent of all cases are now recovering. The seriousness of this group is usually determined by the nature of the local infection that is responsible for the invasion of the blood.

In patients with local or generalized peritonitis with or without abscess formation, 75 per cent of patients have been improved with streptomycin. The same is true of patients with acute cholecystitis or cholangitis with and without bacteremia, or in liver abscesses or pylephlebitis.

The healing of local intra-abdominal abscesses following surgical drainage is accelerated following streptomycin. These abscesses include those in the pelvis following appendicitis, diverticulitis or puerperal sepsis, subhepatic abscesses and subdiaphragmatic abscesses.

Pulmonary infections due to *H. influenzae* have responded extremely well. This is a disease predominantly of infancy and childhood. It is a diffuse bronchopneumonia and is associated with bacteremia in at least 60 per cent of the cases. Eighty-five per cent of patients have recovered. Patients with *H. influenzae* infections associated with laryngotracheobronchitis also respond to streptomycin.

Acute cases of Friedländer's bacillus pneumonia have responded in 80 per cent of cases.

Patients with post-abortion sepsis or puerperal sepsis due to gram negative organisms have recovered in 75 per cent of cases.

Bacterial endocarditis due to penicillin resistant non-hemolytic streptococci or to gram negative bacilli such as *H. influenzae*, *B. coli*, or Friedländer's bacilli have a recovery rate of 30 per cent.

The results in Salmonella infections, in typhoid fever and in undulant fever have been disappointing, since there is no good

and conclusive evidence that the course of these diseases can be changed by the use of streptomycin. Some studies with the combined use of streptomycin and sulfadiazine suggest that these two drugs in combination may be more effective than either one alone.

Streptomycin is the only drug that has a positive effect in tuberculosis in man, but until long term studies can be completed, it is not possible to draw any definite conclusions about the effectiveness of streptomycin in the treatment of this disease.

Side Effects:—

A great deal has been said about the various side effects of streptomycin, and I want to use the rest of my time in discussing this problem.

For purposes of description, the reactions can be divided into 5 main groups: histamine-like reactions, local reactions at the site of injection, sensitization reactions, neurological reactions, and renal irritation. The histamine-like reactions are mainly of historical interest, since they no longer occur. Some of the preparations that were made early in the course of development contained histamine. This substance has been eliminated from the products at the present time.

Local reactions at the site of injection will vary in frequency with the technique of the nurse or physician, and the total amount injected into the muscles. Procaine hydrochloride may be injected along with streptomycin in order to decrease pain. It does not inactivate streptomycin.

Signs of renal irritation have been reported in a few patients and consist of albuminuria and casts. Occasionally nitrogen retention has been observed. An alkaline urine usually causes the casts to disappear. This reaction has been infrequent but it should be looked for in all cases. It is not necessary to stop streptomycin if signs of mild irritation occur.

The two most important reactions are the sensitization reactions and neurological reactions. Skin eruptions and fever are the commonest manifestations of sensitization. They occur in 10 per cent of all patients who receive the drug for 7 to 10

days or longer. It occurs in less than 10 per cent of patients who receive less than 2 grams a day, and in 15 to 20 per cent of those receiving more than 2 grams a day. In brief, it can be said that the incidence of these reactions can be correlated with the daily dose and with the duration of treatment. In many cases the reaction is not severe enough to necessitate discontinuing the drug. The reactions last from a few days to a week or ten days in the vast majority of patients. As far as is known, these reactions cause no permanent damage. That they are due to sensitization to streptomycin receives support from two observations: first, a recurrence of fever and skin eruption may occur following a test dose in a patient who has had a reaction; second, a number of patients have an eosinophilia.

The neurological reactions are perhaps the most important, and they have occurred in the collected experience in 6 per cent of all patients. Five per cent of patients have developed vertigo, two per cent tinnitus and one per cent deafness.

The incidence of neurological disturbances is definitely related to the daily dose and duration of treatment. The smallest number of reactions are observed when 1 gram or less is given daily; that is, in 4.5 per cent. When 1.5 to 2 grams are given, reactions occur in 7 per cent; 2.5 to 3 grams, 14 per cent; and 4 to 5 grams, 22 per cent.

Deafness has been observed when large doses are given intramuscularly for several days; that is, 5 to 6 grams a day, or when large doses are given intrathecally for the treatment of meningitis, or when renal insufficiency is present. It is often permanent, but improvement occurs in a number.

Vertigo is the most frequent and it is very disturbing. It has occurred in 5 per cent of all cases reported to us. The occurrence of this symptom can be correlated with the daily dose and the duration of treatment. It is encountered only rarely when streptomycin is given in amounts of 1 to 2 grams a day for 7 to 10 days. When treatment is prolonged to 3 or 4 weeks or longer, then one encounters the highest number of reactions. Reactions may be negligible, moderately severe or severe. The acute form lasts 7 to 10 days; the minimal signs last 60 to 90 days and then disappear.

CO-RELATOR.

Dosage of Penicillin in Childhood.By Professor **Gino Frontali.**

Director of the Pediatric Clinic, Rome University.

The problems connected with the dosage of penicillin in the different ages of childhood are still a matter for discussion. Research has been carried out in our clinic to clear up this point, and the results have been communicated partially to the Rome Medical Academy since July 1946.

Preliminary experiments were made to ascertain (with Abraham's method, 1941) which *concentration* of penicillin was necessary to inhibit the development in broth, of penicillin-sensitive germs, isolated from our small patients and which concentration of penicillin was necessary to inhibit development of transplantations. The first concentration then, was considered bacteriostatic, and for fourteen strains of *Staphylococcus aureus* varied from 0.03 to 0.50 U/cem, while the second concentration was considered bactericidal and for the same varied from 0.06 to 1.00 U/cem. (See fig. 1).

In other experiments it has been shown that penicillin in certain concentrations, in *contact with blood, plasma, serum and exsudates*, at temperatures of 0°, 20°, 37° C, loses its activity to a certain extent (varying according to the manufacturer, also) but in all cases, with the same temperature, the reduction of activity is greater and faster in these organic fluids, and above all in pleural and meningial pus, than in a physiological saline solution.

We tried then to establish (Midulla) the *dose* of penicillin given intramuscularly, *required* to produce concentrations in the blood sufficient for efficacious bacteriostatic and bactericidal effect, and the period of maintenance of this condition. With Fleming's method of capillary tubes (1945) were obtained the results expressed in fig. 2. In all cases the highest concentration was obtained fifteen minutes after the injection already. After one hour there was a constant lowering to 1/4, 1/8, and even 1/16 and then

CEPPI DI STAFILOCOCCO AUREO															STREPTOCOCCO EMOLITICO
1	2	3	4	5	6	7	8	9	10	11	12	13	14		
OXFORD	I II	I II	I II	I II	I II	I II	I II	I II	I II	I II	I II	I II	I II	I II	
1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0
0.5	-	-	-	-	+	-	-	-	+	-	-	-	+	-	-
0.125	-	-	-	-	+	+	-	-	+	-	+	-	+	+	-
0.0625	-	+	-	-	+	+	-	-	+	-	+	+	+	+	+
0.03125	-	-	+	-	+	+	-	+	+	+	+	+	+	+	+
0.015625	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
0.0078125	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
0.00390625	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
0.001953125	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CONTROLLO	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
A	0.03	0.06	0.06	0.06	0.06	0.06	0.125	0.125	0.125	0.25	0.25	0.25	0.5	0.007	
B	0.06	0.125	0.125	0.5	1	0.5	0.125	0.125	1	0.125	0.5	0.5	1	0.5	0.25
CALIBRATO	12.5	10	12	—	—	—	12.5	—	9	12.5	10	—	—	—	—
CONCENTRATO	16	16	12	—	—	—	12.5	—	14	14	14	—	—	—	—
ANALISI	16.3	12.4	12.3	—	—	—	17.2	—	11.5	11.6	12.6	—	—	—	—

PER I CEPPI DI STAFILOCOCCO AUREO:

I = CULTURE MADRI

II = TRAPIANTI

— = BRUGO LIMPIDO

2 = BRUGO CON UN CERTO GRADO DI OPACITÀ

4 = BRUGO TORBIDO

9 = CONCENTRAZIONE NON SAGGIATA

10 = CONCENTRAZIONE MINIMA INIBENTE

16 = CONCENTRAZIONE NON PERMETTENTE ULTERIORE SVILUPPO NEL TRAPIANTO.

PER IL CEPPETTO DI STREPTOCOCCO EMOLITICO:

— = ASSENZA DI EMOLISI

+ = PRESENZA DI EMOLISI

— } NEI TRAPIANTI = COME PER I CEPPI DI STAFILOCOCCO AUREO

+ }

Fig. 1. Bacteriostatic and bactericidal penicillin concentrations on 14 strains of *Staphylococcus aureus* and 1 of *Streptococcus haemolyticus*.

a more or less sharp fall to zero between the 2nd and the 3rd hour or the 3rd and 4th.

In children with high fever (over 38° C) no earlier reduction or disappearance of penicillin was to be noted than without fever.

Considering the *weight* of subjects examined, the vertex and the lowering curve of penicillin concentration, in the blood, are generally, for equal doses, in inverse proportion to the weight of the body, with exception for those weights slightly differing from each other, and some individual peculiarities (fig. 3, 4, 5, 6). For the same dose (5—10—15—30 000 U.) the lowest curve corresponds generally to the highest weight and so reciprocally.

TAVOLA RIASSUNTIVA N. 1°

CONCENTRAZIONI DI PENICILLINA NEL SIERO DI SANGUE DI BAMBINI DOPO SOMMINISTRAZIONE INTRAMUSCOLARE DI DOSI VARIE DEL FARMACO.

SOGGETTI IN ESAME				TITOLO DEL SIERO						
N.	NOVE ETA'	PERO KG	DIAGNOSI	INIEZIONE UN.	IN UNITA'	OKFORD	PER	CC.		
					005	005	020	030	040	050
					15	30	45	60	75	90
CONVALESCENTI O CON MALATTIE AFEBRILI										
1	O.C. M.25	1.9	DISTROFIA	2,000	2	1	0.25	0.125	0.06	-
2	L.O. M.7	4.5	DISTR. NACH.	5,000	1	0.25	0	0	-	-
3	C.R. M.9	6.3	INTOSS. ALIM.	6,500	8	1	0.03	0	0	-
4	M.M. A.2	0.4	PAR. POSTDIFT.	4,000	0.25	0.03	0	0	-	-
5	D.A.L. A.55	12.	NAN. IPOFISAR.	15,000	8	0.5	0.125	0	-	-
6	C.M. A.5	16.	POLINEURITE	15,000	1	0.125	0	0	-	-
7	O.E. A.5	16.6	WERLHOF	10,000	1	0.06	0	0	-	-
8	P.M. A.5	17.	ESITI NOMA	17,000	4	0.5	0.25	0	-	-
9	V.G. A.8	21.	NEOPLASIA	21,000	4	2	0.25	0.03	0	-
10	C.L. A.12	24.4	PELLAGRA	30,000	4	0.5	0.125	0	-	-
11	A.A. A.10	25.4	MIOPATIA	10,000	0.25	0.03	0	0	-	-
12	A.A. A.10	25.4	ID.	20,000	0.5	0.06	0	0	-	-
13	A.A. A.10	25.4	ID.	30,000	4	0.5	0.03	0	-	-
FEBBRICITANTI										
14	M.M. M.7	5.2	ENTEROCOLITE	5,000	4	0.25	0.06	0	-	-
15	L.F. M.8	8.	BRONCOPOLM.	8,000	4	1	0.25	0.03	0	-
16	R.F. A.8	16.1	PERIT. TBC	5,000	0.5	0.125	0	0	-	-
17	R.F. A.8	16.2	ID ID	15,000	4	0.25	0.03	0	-	-
18	V.F. A.11	20.5	NEUM. ANT. AC.	30,000	2	0.25	0.03	0	-	-
CURATI CON PENICILLINA										
19	S.A. M.25	3.1	ERESIPELA	2,000	2	1	0.5	0.5	0.25	-
20	R.F. A.2	8.5	FRATT. CRANIO	10,000	4	1	0.125	0	-	-
21	R.A. A.3	11.4	EMPIEMA	10,000	1	0.06	0	0	-	-
22	A.V. A.6	15.	CISTI SUPPUR.	12,500	0.25	0.06	0	0	-	-
23	B.C. A.55	17.	OSTEITE CRAN.	15,000	4	2	0.25	0.06	0.03	-
24	C.L. A.6	18.2	OSTEOMIEL.	10,000	1	0.125	0	0	-	-
25	V.L. A.9	20.	ID.	20,000	2	0.5	0.125	0	-	-
26	L.G. A.9	25.	ID.	25,000	2	0.5	0.125	0	-	-
EFFETTI DA DEFICIENZA RENALE										
27	P.A. M.15	3.8	STEN. PILODO	10,000	4	1	0.5	0.25	0.125	0.06
28	G.G. M.11	6.	INTOSS. ALIM.	2,000	1	0.25	0.03	0	-	-
29	R.L. A.55	25.1	NEFROSI	5,000	0.5	0.25	0.25	0.25	0.125	-
CARDIOPATIE										
30	R.D. A.6	17.	INSUF. AORT.	5,000	2	0.25	0.03	0	-	-
31	F.A. A.8	23.6	VALV. REUM.	5,000	2	0.125	0.03	0	-	-
CON AZIEZIONI EPATICHE										
32	F.D. M.34	4.8	OCCL. VIE BIL.	10,000	2	1	0.5	0.125	0.06	0
33	P.R. A.11	27.5	EPAT. ITTERIC.	25,000	4	0.5	0.125	0.06	0.03	-

Fig. 2. Concentrations in the blood serum of children at different intervals after intramuscular injection of various doses of penicillin (maximum after 15 minutes).

Studying the effect of *increasing dosage* in the same subject, the curves reach a higher level and show longer period of persistence of penicillin in the blood as shown in fig. 7.

When doses, corresponding to 1 000 U. per kilogram were injected intramuscularly in children weighing from 1.9 kilograms to 29.5 kilograms the medium curve shown in fig. 8 was obtained, with a vertex of 3.22 U/cem after fifteen minutes, descending to

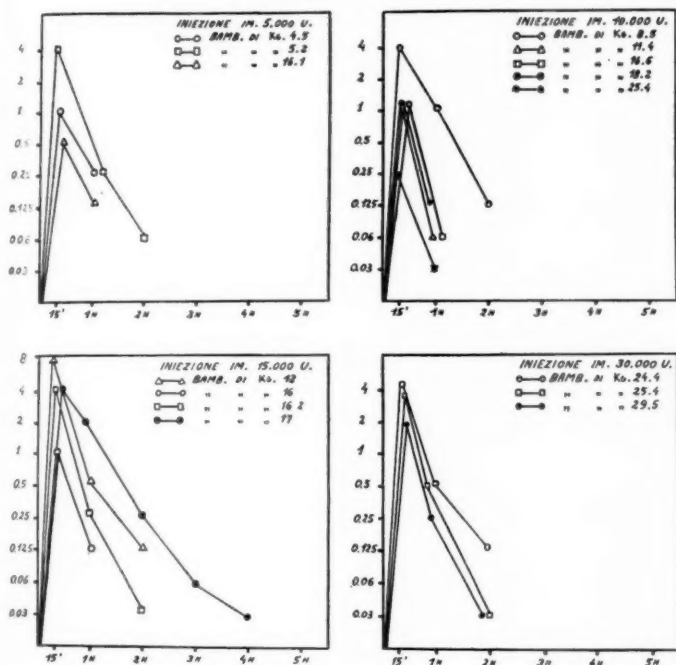


Fig. 3—6. Blood serum concentration curves in children with different body weight after intramuscular injections of 5 000, 10 000, 15 000, 30 000 units.

1/4 after one hour, to 1/20 after two hours and to 0.02 U/cm at the third hour.

It is worth remarking that for *infants under three months* the curve descends more slowly than in older children, so that after four hours, for small doses (2 000 U.), concentrations of 0.25 to 0.06 U/cm are found (see fig. 9).

In *nephropathic patients* with reduced excretion of urine (about 1/4 normal), high concentrations of bacteriostatic value were obtained with small doses and prolonged to the 4th or 5th hour (fig. 10).

In children with *obstructive jaundice* bacteriostatic concentrations for medium doses were maintained up to the 4th hour (fig. 11).

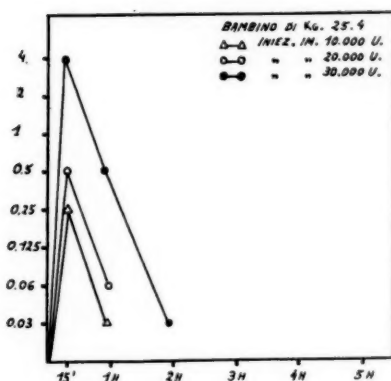


Fig. 7. Blood serum concentration curves in the same child after increasing doses of penicillin intramuscularly injected.

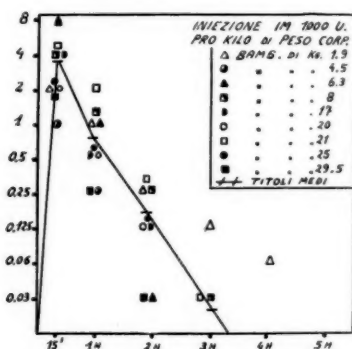


Fig. 8. Medium curve of blood serum concentration when doses corresponding to 1000 units per kg body weight (varying from 1.9 to 29.5 kg) are injected intramuscularly.

From these results it may be assumed that children over three months, with normal liver and kidney, require 1000 U. per kg every three hours to reach variable concentrations in the blood which, in the first 60—90 minutes will be bactericidal and up to $2\frac{1}{2}$ —3 hours bacteriostatic for the standard *Staphylococcus* and for the more sensitive germs. For organisms that — though

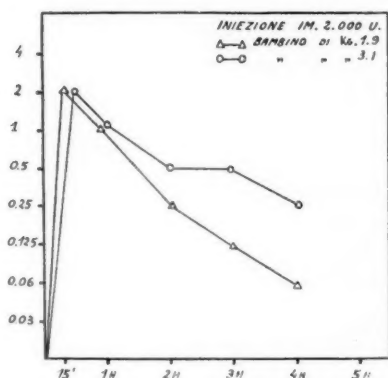


Fig. 9. Blood serum concentration in infants under 3 months of age.

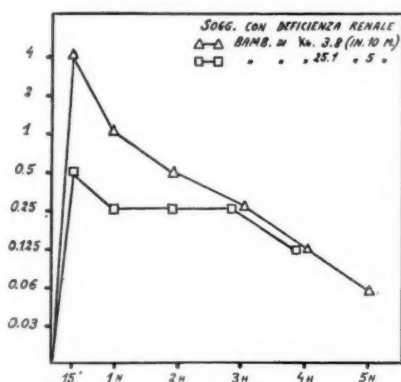


Fig. 10. Blood serum concentration in nephropatic subjects.

sensitive — are more resistant, these doses should not be applied without revision.

Therefore the dosage proposed by Bodian (1946) of 2 200 U. per kg every twenty-four hours for infants under one year to be given every 4 hours, seems not sufficient for maintaining a bacteriostatic level after the second hour in infants over three months.

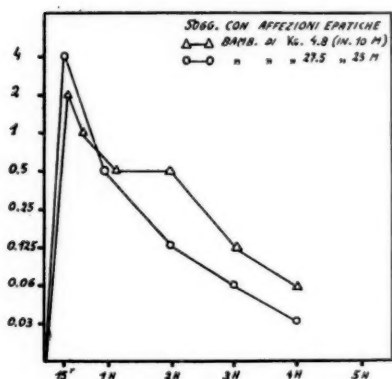


Fig. 11. Blood serum concentration curve in children with obstructive jaundice.

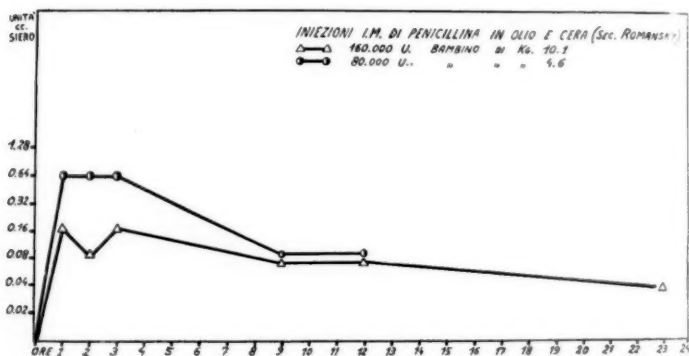


Fig. 12. Blood serum concentration curve in children after intramuscular injection of penicillin in oil and wax solution.

Buchanan too (Oct. 1946) finds Bodian's dosage insufficient and concludes that doubled quantities, and even 4 times as much, are required to combat less sensitive germs, reaching thus a dosage slightly differing from the one already proposed by us (in July 1946).

Recently, using penicillin in oil and wax solution, more stable concentrations were obtained reaching the maximum after one

hour and having a much slower rate of lowering with bacteriostatic values (0.08 U/ccm) after 12 hours and even (0.04 U/ccm) after 23 hours (fig. 12).

Comparing the doses for 24 hours in the 2 methods, double of the quantity was required when using oil and wax solution.

Clinically therapeutic success may be obtained too, with smaller doses, but in this case we must depend on Bigger's theory which claims that the *intermittent method* is useful in order to bring about

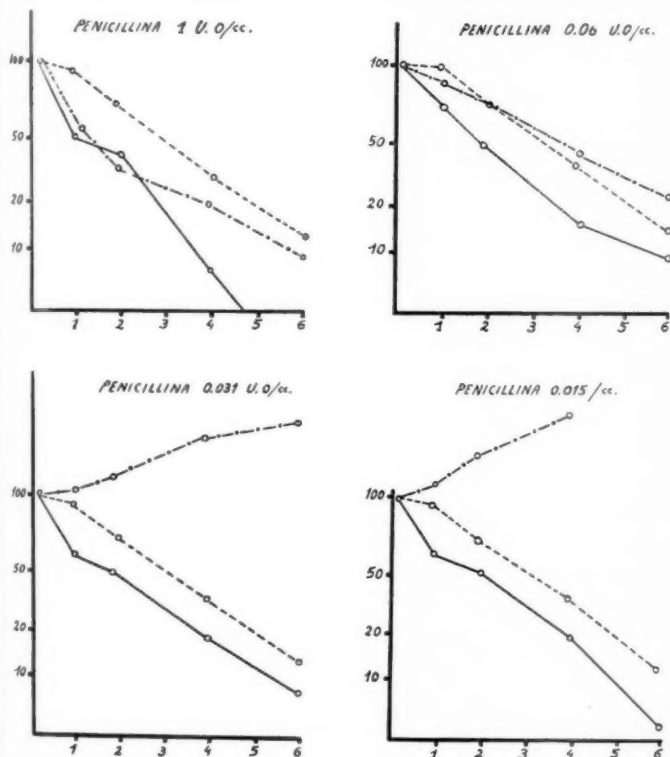


Fig. 13—16. Bactericidal activity of the blood added to progressively lowering concentrations of penicillin (higher curve) with resulting more efficacious action on the multiplication of haemolytic streptococci than would result by addition of the effect of either agent (Morra).

bactericidal concentration in the blood, with the aim of striking at the germ to be overcome at the phase of the logarithmical multiplication. Or else there is the *bactericidal activity of the blood* to be counted on, which added to that of the penicillin has, according to Morra, a more efficacious action on haemolytic streptococci than either of these agents taken separately, so that even weak concentrations of penicillin, not bacteriostatic, become bactericidal when working in cooperation with the bactericidal power of the blood (see fig. 13—16).

It is well known that concentrations of penicillin diminish much less rapidly in the fluids contained in *closed cavities* (pleural cavity and the arachnoid space) than in circulating fluids.

After the intrapleural injection of 15—30 000 U. in children aged $1\frac{1}{2}$ —6 years, when the evacuation of the greatest possible amount of exsudate had taken place, the persistence of concentrations varying between 0.5 and 0.8 U./ccm was found after three days with curves of concentration non dissimilar to that of fig. 17. The variations in individual cases were considered as being in

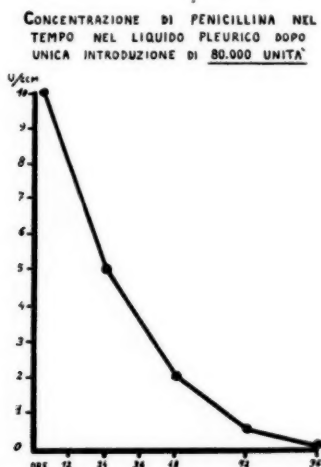


Fig. 17. Penicillin concentrations in pleural exsudate (0—96 hours) after intrapleural injection.

relation to the amount of pus, which in some cases was small (40 ccm. in one case, in which 15 000 U. were sufficient), while in other cases, where 80 000 U. were used, the amount of exsudate was larger (as much as 500 ccm) and reformed rapidly.

It was possible also to show a destruction of penicillin *in loco* since samples of pus kept at 0° C maintained their concentration from ten to fifteen days, while at 37° C it was reduced to 0 in seventy-two hours, that is much faster than in (physiological) saline solution.

Therefore, the doses of penicillin to be injected into the *pleural cavity* and the period to be established between successive doses depends on the quantity of extracted exsudate, on the rapidity with which it is re-formed, on the rapidity of absorption, of penicillin (judged by the concentration in blood and urine), and on the destruction *in loco*.

In the therapy of *meningitis* caused by penicillin-sensitive germs we have first of all examined the possibility of penicillin passing through the blood-fluid barrier following intramuscular injections (Malaguzzi).

Ninety minutes after intramuscular injection of 10 000—40 000 U. were given to children weighing from 3 to 14 kg, concentrations of 0.5—0.7 U/ccm were found in the blood, while in the spinal fluid no evidence of penicillin activity was to be ascertained. In meningitis cases also it was not possible to ascertain the passage of penicillin into the cerebro-spinal fluid, from one to three hours after intramuscular injection. It still remains uncertain whether or not intramuscular injection can exert influence on the persistence of penicillin injected intrathecally.

It was observed by Sansone and Tolentino (Genoa) that in the first three months of life only does penicillin pass in dosable quantities into the cerebro-spinal fluid, after intramuscular injections, in 7 out of 9 cases; in infants up to one year in 1 out of 5 and in no case in infants over one year.

We wished to test penicillin concentrations *immediately* after intrathecal injections — a research, as far as we know, not carried out by others. It was found that for 10—20 000 U. injected, con-

CONCENTRAZIONI DI PENICILLINA
NEL LIQUIDO CEREBRO-SPINALE, DOPO
INTRODUZIONE DI 20.000 U.Ox. ENDORACHIDE

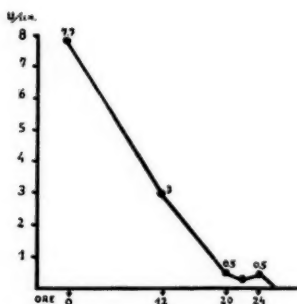


Fig. 18. Penicillin concentrations in spinal fluid (0—24 hours) after intrathecal injection.

centrations were 5—9.5 U/cem, that is much less than we expected, calculating the penicillin as having been diluted in the total quantity of fluid (amounting to 100 ccm according to estimates by Kruse and our own).

After twelve hours, values were found to have descended to 1/3; after 17 hours to 1/6; in no case after twenty-four hours were found as much as 1 U/cem (fig. 18). No penicillinic activity was found in any case after the 26th hour.

Speaking generally, the persistence of higher values and of longer duration has coincided with an improvement of the spinal fluid. There may be two explanations for this: 1) a re-established minor permeability of the blood-fluid barrier, 2) a lower destruction of penicillin *in situ* on account of the reduction of the number of leucocytes and germs.

With regard to penicillinic action on circulating fluids and on fluids in closed cavities, against penicillin-sensitive germs, it seems that the defensive activities of infantile organisms are not damaged. We have already seen the synergic effect of the bactericidal power of the blood and we have yet to speak of the *hematologic picture* and of the *sternal puncture*.

According to our research (Matteucci) carried out in 21 cases with a total of 71 sternal punctures, no lowering effect was found in the functioning of the marrow, even in those cases where after a treatment with sulphonamides, the condition of the blood and the marrow had been damaged.

In all cases, even in those prolonged and fatal, the activity of the marrow maintained its efficiency and has even improved, especially with regard to the granulocytic series. The same observation applies also to a case of erythroblastic anaemia (Cooley type) affected with erysipelas and cured for this infection. The recovery, with regard to the red series, has been slower and torpid, in cases where a more marked sufferance was showed.

The improvement of the hematologic picture and of the marrow activity is to be related not to a direct stimulative effect, but rather as an indirect consequence of the curative effect of the drug on sepsis.

In the short time allotted to me I have tried to trace only some of the practically and theoretically important problems connected with dosages, absorption and concentration of penicillin in organic fluids at different ages of childhood.

CO-RELATOR.

»Gezielte Injektionen» und ihre Rolle in der Chemotherapie.

Von Prof. **Rudolf Degkwitz**, Hamburg, Deutschland.

Es ist möglich Medikamente nach intravenöser Injektion innerhalb des menschlichen Körpers auf ein bestimmtes Organ zu lenken, eine Methode, die man als gezielte Injektion bezeichnen könnte. Dasselbe Medikament kann ausschliesslich auf die Leber, oder die Milz, oder die Lungen, oder auf das Knochenmark, je nach Bedarf, gelenkt werden. Durch Injektion in Körperhöhlen (Bauchhöhle, Pleurahöhle) kann man auf die Mesenterial- oder Hiluslymphknoten hinzielen.

Es ist für solche gezielte Injektionen wesentlich, dass die zu verwendenden Mittel in Wasser unlöslich und kristallisierbar sind.

Sie müssen dagegen in Protoplasma löslich sein. In welchem Organ das Medikament nach intravenöser Injektion abgelagert wird, hängt demnach nicht von den chemischen Eigenschaften der Substanz ab, sondern von ihrem physikalischen Zustand, d. h. von Gestalt und Grösse ihrer Kolloidteilchen bei Dispersion in Wasser.

Wenn man Gewebe oder einzelne Zellen im polarisierten Lichte untersucht, so findet man kristallinische oder kristalloide Gebilde (Muskelfibrillen, Nervenfasern, Chromosomen, etc.). Es gibt eine bestimmte Gruppe von Verbindungen innerhalb des Protoplasmas — die wasserlöslichen Lipoide — die die Bildung von Kristallen begünstigen, während eine andere Gruppe — die wasserlöslichen Proteine und Kohlehydrate — die Kristallisation verhindert.

Mit Hilfe dieser zwei antagonistischen Systeme kann man in vitro aus demselben Mittel Kügelchen, Nadeln, Flocken und Fasern von ganz bestimmten Durchmessern erzeugen, indem man die Substanz zuerst kristallisieren lässt und dann nach einer gewissen Zeit den Kristallisationsprozess unterbricht.

Kügelchen und Teilchen von bestimmten Durchmessern werden nach intravenöser Injektion von der Leber, Milz oder Knochenmark aufgespeichert. Nadelförmige Teilchen mit einem Längsdurchmesser von 10 Mikron (ähnlich dem eines roten Blutkörperchens) werden in der Lunge stecken bleiben. Kugelförmige Teilchen werden nach Injektion in Körperhöhlen von den Lymphgefässen weiter befördert und sammeln sich in den Lymphknoten an.

Kolloidale Teilchen von Azofarbstoffen, die in Wasser unlöslich, dagegen in Fetten und Protoplasma leicht löslich sind, wie z. B. Anilin-Azodimethylanilin oder Anilinazobetanaphthol, töten Tuberkelbazillen in Kulturmedien, in denen sie in einer Verdünnung von 1 : 40 000 aufgeschwemmt sind.

Wenn man Meerschweinchen durch Injektion von ungefähr 40 000 Tuberkelbazillen infiziert und danach einmal wöchentlich mit einem der oben erwähnten Farbstoffe, die in Form sehr kleiner Kügelchen im Wasser verteilt sind, spritzt, so überleben die Versuchstiere nach sechs bis sieben Wochen Behandlung, während die Kontrolltiere innerhalb dieser Zeit sterben.

Discussion.

Dr. Andor Bosányi, Budapest, Hungary.

First, I would like to tell you, that both penicillin and the new sulfamid compounds, such as sulfothyasol, and sulfodiazine, were supplied to us shortly after the armistice by Colonel Shackleford, for the time Medical Adviser to the American Military Mission, who also took pains to supervise and direct our first tryouts with these drugs. This was one of the very first gestures of the American Occupational Army toward us, and I can assure you, that many monuments stand in quite a few Hungarian hearts, with the inscription: Many thanks to the U. S. A.

There is no time for me to give you detailed statistical account of all my cases treated effectively with penicillin alone or in combination with sulfonamides; instead of this I am going to put up the question why in certain number of cases one does not see any effects from either of these drugs.

I will select three main groups of diseases. These are:

1. bronchopneumonias,
2. meningitis,
3. septic cases of scarlet fever.

On the first place stand 54 cases of bronchopneumonias developing in the course of laryngeal or tracheobronchial diphtheria. Under 2 or 3 years of age, this disease proved to be fatal in about 45—50 % owing to the fact that in about two thirds of the cases bronchopneumonias will develop very early and spread with malignant rapidity. With the use of penicillin and later in combination with sulfamids fatality rate diminished to 28 %. 20 cases were lost in spite of prolonged treatment, which was started right at the first signs of pulmonary involvement, whereas 5 cases received penicillin preventively, 3—5 days prior to any pulmonary involvement. In all cases lost, the inflammation progressed just as if no treatment would have been employed, and there was a wide dissemination of foci of the size of a peanut. In three instances these foci suppurated and at post-mortem in one of the cases a pulmonary abscess was seen in the right middle lobe of a magnitude of an egg. Whenever it was feasible, microscopic and cultural examinations of the excreted sputa were performed during life, revealing different strains of pneumococci and haemolytic streptococci, and what was most astonishing in five of these cases the strains prove to be nonresistant to penicillin in vitro.

Maybe some kind of respiratory viruses have played also a role with these inflammations, however macroscopic as well as microscopic findings were not at all different from the most common type of bronchopneumonias.

The second group consists of 11 cases of meningitis treated solely

with penicillin given intrathecally as well as intramuscularly, out of which I lost three cases. In two of these cases haemolytic streptococci, in one pneumococci were revealed in the spinal fluid. In all the cases treated there was a rapid improvement in the beginning, and spinal fluid became clear and sterile soon. Treatment was not discontinued for another ten days, yet in three cases there came a turn to worse. Although spinal fluid as well as cysternal fluid remained clear and sterile, high fever of an intermittent type and increased intracranial pressure persisted, and in spite of continuation of the treatment, marasmus followed, the same which we were used to know before. At post-mortem no other pathological changes were to be seen than subacute inflammatory involvement of the meninges. The assumption of a superimposed virus acting similarly as with the bronchopneumonic cases, does not seem to be feasible.

The third group consists of several cases of septic scarlet fever, known as suppurative complications. In all there was mastoid involvement, and mastoidectomy was performed. Three out of 21 cases died in spite of prolonged treatment with penicillin and sulfodiazin. Blood cultures were negative for haemolytic streptococci, also the slight discharge from the mastoid wound became sterile after the administration of one million units of penicillin, the whole course of the cases strongly resembling chronic cryptogenetic septicaemia. Though evidence is lacking, the possible role of another undetected microorganism resistant to penicillin can not be excluded.

I am afraid that in our efforts aimed to control the microbes we well nigh identify microbes with the disease itself. Perhaps we overemphasize and overestimate the role of invading microorganisms, believing that epidemics can be aroused simply by a sudden spread of numerically increased pathogenic microbes, or by an increase of their virulence. I am going to mention only one fact which contradicts such an assumption. I think everyone of us knows that during meningitis epidemics we observe cases simultaneously and nearly in equal numbers of quite different etiology and the bacteriologic findings may vary between streptococci, pneumococci, meningococci, tb. bacilli, besides which there are so-called sterile cases of virus meningitis. Do we have the right to say that for an outbreak of an epidemic all these microorganisms are responsible, developing increased pathogenic ability just around the same season of the year? Is it not wiser to believe that in starting epidemics beside the different microbes an intrinsic human factor is equally responsible? — And if so, how can we still believe, that all or the best we can do in order to cure infectious diseases is nothing else but to control microbes or neutralize their products?

I definitely do not deny the great value of potent antibiotics and chemotherapeutics, and I regard equally important immunotherapy. Nevertheless I think that we know little about an intrinsic factor

which seems to play a role as important in infectious diseases as the microbes themselves. This factor was known long before the discovery of microbes by the great scientist Sydenham as epidemic constitution, and I wish to express my believe, that at one of the next paediatric congresses more attention will be paid and more research will be done on this undoubtedly existing important factor.

Dr Manuel Suárez, Zaragoza

se refiere en primer término a la quimioterapia de la fiebre de malta, exponiendo observaciones personales en que la curación fué obtenida por sulfamidas tipo tiazol y otros con estreptomycin. Estos resultados son mejores que los obtenidos en Estados Unidos, lo que hace pensar en distinta sensibilidad de las brucelas a estas drogas. En la fiebre tifoidea los resultados con la asociación sulfamidas-penicilina a grandes dosis, inspirado en los trabajos de BIGGER, son favorables y es aconsejable su empleo. Respecto al problema del tratamiento de la meningitis tuberculosa es prematuro dar conclusiones, pero no puede negarse el efecto beneficioso de la estreptomycin cuando es patente el hecho de la prolongación de la vida de estos enfermos, condenados antes irremisiblemente a la muerte en poco tiempo, sin olvidar los casos de curación, aun cuando sea con secuelas. A nuestro juicio, dos problemas fundamentales plantea esta terapéutica: por un lado se precisa un diagnóstico muy precoz y determinar en lo posible la forma anatomoclínica; por otro, llegar a un acuerdo sobre la técnica de administración, pues todavía no está claramente establecida la dosis, duración del tratamiento, ni el momento en que ha de suspenderse, etc. Puede haber casos en que no sea preciso la vía intramuscular utilizando únicamente la intrarraquídea con el ahorro consiguiente de droga y evitación de posible intoxicación, pero en otros la ruta intramuscular deberá ser empleada más o menos tiempo asociada siempre a la intratecal, según la forma anatomoclínica. La conducta a seguir la decidirá en cada caso la clínica y el control del liquor.

Prof. Wilfrid Gaisford, M. D., F. R. C. P., Manchester University, England.

Infectious diarrhoea may be enteral or parenteral in origin. In either case chemotherapy may well be instituted, sulphadiazine, sulphaguanidine or succinyl sulphathiazole being prescribed in fairly large doses.

During their dissociation in the body the sulpha drugs produce an acidogenic effect which must be of some importance. What is the practical effect of therapeutic doses on the acid-base equilibrium in these cases of diarrhoea and what allowances should be made to counteract it?

The paediatricians from Europe who have been privileged to visit a number of paediatric centres in the U. S. A. have all been impressed by

the work being done and the progress made in studying the restoration of electrolyte equilibrium in diarrhoeal conditions. Now, important though rehydration is, it cannot be adequately accomplished and maintained in the presence of a continued parenteral infection, so that the effect of the sulpha drugs used to treat such infection must be taken into account in deciding on the composition of the rehydrating solution.

Now I would like to make a plea for the more conservative treatment of meningitis. As, in treating diarrhoea, the infant is more important than his stools, so in meningitis the child is more important than his cerebrospinal fluid.

With the introduction of the sulpha drugs the prognosis of meningococcal meningitis was completely altered and that of pneumococcal meningitis greatly improved. With the advent of the antibiotics, *H. influenza*, streptococcal and pneumococcal meningitis have all responded. Powerful neutral salts of sulphapyridine and sulphadiazine are now available for intravenous and intramuscular injection and, together with oral sulphadiazine and with penicillin and streptomycin should, given early enough in the disease and in adequate dosage, obviate the need for intrathecal therapy in these types of meningitis unassociated with surgical or traumatic conditions.

Only one lumbar puncture is necessary, and that for diagnostic and sensitivity purposes.

The treatment is, essentially, intensive systemic chemotherapy, absolute quiet, enough sedative to keep the child drowsy throughout his acute phase, and hypertonic rectal salines, as necessary, to relieve headache from the increased intracranial tension.

Limiting the amount the child is disturbed is an important part of the treatment. Thus, repeated lumbar punctures are bad and intrathecal therapy worse.

Sterilisation of the cerebrospinal fluid is by no means synonymous with clinical cure. I believe that if the child's clinical condition is satisfactory the state of his cerebrospinal fluid may well be ignored.

Routine intrathecal injection in all sorts of meningitis, now practised generally in many hospitals, is a retrograde step in therapy. It should be resorted to only in exceptional circumstances and after careful consideration of each individual case on its merits.

Plenary Session—Neonatal Mortality.

RELATOR.

Neonatal Mortality.

By **Alan Moncrieff**, M. D., F. R. C. P.

Nuffield Professor of Child Health, University of London.

For several reasons during the past few years the subject of neonatal mortality — deaths in the first four weeks of life — has been much discussed in Great Britain. The man-power situation during the war and the stark fact of a diminishing birth rate, leading to the setting up of a Royal Commission on Population, prompted an inquiry into the wastage occasioned by the loss of infant life. A distinguished statistician (R. M. Titmuss) estimated that out of nearly two million pregnancies in England and Wales during the three-year period 1936—38 more than a quarter of a million or 1 in 8 failed to result in a child alive at the age of one year. To some extent the whole subject had been obscured by a steadily falling infant mortality rate — that is deaths during the first year of life per thousand live births. A steady decline from well over the hundred mark at the beginning of the century to under fifty to-day, a reduction of about two-thirds, has been accepted as evidence of excellent progress in the field of infant hygiene and preventive medicine — as of course it is. But detailed analysis of the deaths in the first year of life soon reveals that the progress has been uneven and that the neonatal period does not record so good a performance as in the next eleven months. It is with this period that we are concerned to-day.

Table I shows the trend of neonatal mortality in England and Wales. These figures for the whole country, however, again obscure what is revealed by more detailed analysis.

TABLE I. Trend of Neonatal mortality, England and Wales, 1906—1944.
Deaths under four weeks per 1 000 live births.

1906—10.....	40	1938.....	28
1911—15.....	39	1939.....	28
1916—20.....	37	1940.....	29
1921—25.....	33	1941.....	29
1926—30.....	32	1942.....	27
1931—35.....	31	1943.....	25
1936.....	30	1944.....	24
1937.....	30		

TABLE II. Neonatal mortality rates by region, Great Britain, 1944.

England and Wales.....	24
Greater London.....	22
Remainder of South East.....	23
East.....	22
South West.....	22
Midlands.....	24
North.....	27
Wales.....	27
Scotland.....	32

Table II for example shows remarkable differences for different parts of the country and to complete the picture as revealed to us in Great Britain in recent years I show a table covering the pre-war period for certain selected countries. Since this is an international congress I shall look forward to hearing what our colleagues from these other countries have to tell us.

TABLE III. Neonatal mortality rates for certain countries, 1934—38.

Holland.....	22	England and Wales.....	30
New Zealand.....	23	U. S. A.....	32
Norway.....	23	Canada.....	34
Australia.....	27	Scotland.....	37

In any discussion of neonatal deaths it is necessary to take some account of stillbirths and here at once a difficulty is encountered, especially in any attempt at international comparisons. In Europe pulmonary respiration is accepted as a sign of live birth and hence if the heart is beating but the infant never breathes, this is recorded as a «dead birth». In Great Britain on the other hand the presence of a beating heart after birth is accepted as a sign of life even if no breathing occurs. It follows that more infants are likely to be recorded as stillborn (or «deadborn») in Europe than in Great Britain, and conversely the neonatal mortality rate is for this

reason likely to be lower on the Continent and higher in Great Britain.

With these facts in mind let me now present the problem in round figures as we see it to-day in Great Britain. For England and Wales we have about 600 000 births a year. Of these there will be about 25 000 stillbirths and 35 000 deaths in the first year, of which 18 000 will occur in the first four weeks. The total loss of infant life therefore is in the neighbourhood of 10 per cent. Since at present the »natural increase», or excess of live births over deaths at all ages, is about 119 000 a year, the loss of 60 000 is obviously of the utmost seriousness. (Woolf, 1946). (Moreover these figures take no account of the loss of lives by abortion — that is pregnancies terminating before the 28th week).

Next let us look at the more detailed analysis of neonatal deaths. The most recent figures available have been kindly supplied by Dr. Percy Stocks of the General Register Office and refer to 1945.

TABLE IV. Extracts from Vital Statistics for 1945 by courtesy of Dr. Percy Stocks, General Register Office, England & Wales.

Inter. List No.	Causes of Death	Total under 4 weeks
	All Causes.....	16 910
106	Bronchitis.....	111
107—9	Pneumonia (all forms).....	838
119	Enteritis & Diarrhoea.....	502
157	Congenital Malformations.....	2 372
158	Congenital Debility.....	348
159	Premature birth.....	7 116
160	Injury at birth.....	1 785
	a) Intra-cranial or spinal haemorrhage due to injury at birth.....	1 287
	b) Other intra-cranial or spinal injuries at birth.....	67
	c) Other birth injuries.....	431
161	Other diseases peculiar to the first year of life....	3 002
	a) Asphyxia during or after birth, atelectasis.....	1 866
	b) Intoxication due to maternal toxæmia.....	270
	c) Infections of the new-born.....	97
	c 1) Infections of the umbilicus.....	27
	c 2) Pemphigus neonatorum.....	30
	c 3) Other or unspecified infections included under (c).....	40
	d) Melæna neonatorum.....	257
	e) Other specified diseases included under 161.....	512
	e 1) Haemolytic diseases of the newborn.....	457
	e 2) Other diseases included under 161 (e).....	55
	Other Causes.....	836

There is obviously not time to discuss much of this table in detail but before taking up certain points there are certain, general comments to make about trends. For some time now all vital statistics in Great Britain have been analysed in relation to social class, broadly deduced from the occupation of the father in the case of infants. This gives five social classes which are set out in Table V.

TABLE V.

Social Class	Description of Class
I	The professions, commissioned officers and well-to-do people concerned with finance, shipping, etc.
II	Intermediate between Class I and skilled workers
III	Skilled workers
IV	Intermediate between skilled and unskilled workers
V	Unskilled workers

If now we apply this grading to a typical pre-war period for neonatal mortality we get a table which at once reveals certain disquietening features.

TABLE VI. Mortality from Congenital Causes for Legitimate Infants by Social Class of Father, England & Wales, 1930-32.

Social class	I	II	III	IV	V	All
Congenital malformations.....	5.0	5.4	5.6	5.7	5.4	5.5
Congenital debility.....	1.4	2.2	2.9	3.3	3.8	3.0
Premature birth.....	10.5	14.4	16.8	18.6	19.6	17.3
Injury at birth.....	2.3	2.5	2.1	2.0	2.0	2.1
Other Causes.....	2.8	3.0	2.7	2.9	3.0	3.0
Total	22.0	27.5	30.1	32.5	33.8	30.9

This shows that the total mortality in Class V is about 50 per cent higher than in Class I and that whereas congenital malformation as a cause of death shows no class gradient there is a steep rise for premature birth and congenital debility which suggests a connexion with poverty. (There is a statistical point here which should be noted. There are fewer children born to families in Class I, a larger number of first-borns appear in this group with the well-known increased hazards for the first baby and that if anything this class is weighted adversely which makes the comparison even more striking).

The fact that economic considerations affect the mortality rate

TABLE VII. Extract from Vital Statistics for 1945 by courtesy of Dr. Percy Stocks, General Register Office. Deaths in Early Life. (England and Wales.)

Causes of Death	Total under 4 weeks	Under 30 minutes	30 minutes and under 1 day	Total under 1 day	Days						1 day and under 1 week	Weeks			
					1	2	3	4	5	6		0	1	2	3
All causes															
M. & F.	16 910	874	5 270	6 144	1 892	1 531	1 081	645	575	438	6 162	12 306	2 084	1 385	1 135
Premature															
M. & F.	7 116	260	3 048	3 308	967	637	361	238	200	160	2 563	5 871	673	363	209

gives rise at once to obvious lines of action. Undernutrition and overcrowding are the principal elements in the lower income groups which could contribute to the poorer statistics. Both are amenable to social measures and indeed during the war of 1939—45 improving nutritional conditions for the lower income groups in Great Britain probably represented a valuable experiment, for the neonatal mortality rate continued to fall — and the stillbirth rate, not likely to be influenced by housing conditions, fell even more steeply, despite many special adverse factors.

Premature birth accounts for the largest single group of neonatal deaths and must be considered in more detail. The first thing to note is that death in the majority of prematurely born infants occurs so early that it is the obstetricians rather than the paediatricians who must help in reducing the death-rate by preventing the too early termination of pregnancy. Table VII is abstracted from figures also kindly supplied by Dr. Percy Stocks. Nearly half the deaths ascribed to premature birth (3 308 out of 7 116) are in infants who survived less than twenty-four hours and over another third are dead in the first week. It follows that any plan to deal more effectively with premature babies must secure early and prompt action. A special committee of the Ministry of Health in London investigated this problem in 1943, and made important suggestions for improving the care of these infants both in hospital and in the home. In order to secure that the

medical officers of health should have early knowledge of these babies it was suggested that the weight at birth be added to the «notification of birth» card which must by statute be sent to the health office within 36 hours of every birth by the father or someone in attendance on the mother. It is too early yet to know what reduction in deaths from prematurity can be achieved for the country as a whole when the measures advocated are put into practice. A model scheme has been worked out for the City of Birmingham (Crosse, 1945) and other centres are following as fast as building and staff difficulties permit.

The figures for asphyxia and birth injury taken together represent the next largest group (1 866 and 1 785 respectively in the 1945 list — Table IV). Regarding the latter Gale (1947) has pointed out that the deaths ascribed to birth injury actually exceed the total deaths in childhood up to the age of 15 from motor car accidents, about which there is quite rightly much public anxiety. In both these groups better medical and nursing care would probably effect some reduction. In Table II the lower rates shown for Greater London may as Woolf (1946) has suggested be related to a higher standard of medical and nursing care available. If this group is to be improved it will be achieved by education. Prof. C. McNeil, who in an early review of the subject (1942) started many of us thinking, puts all the emphasis — as a Scot always must and will — upon the factor of education. His advocacy of «child health training schools» is already bearing fruit and there are today seven holders professorial chairs in England and Scotland where the title of the chair and the emphasis of the work done indicates that preventive paediatrics is being increasingly taught and a closer linkage between hospitals and well-baby clinics is being steadily achieved. Time does not permit of more details being given. It must be sufficient to say that a University Institute of Child Health, such as I have the honour to direct in London, represents a somewhat delayed academic recognition of the supreme importance of the subject.

To return to the principal causes of neonatal death, a word must be said about congenital malformations, the next largest single group in the 1945 figures (2 372). It is a general experience

that as other causes of neonatal mortality are reduced so this cause assumes a relatively greater importance. According to Woolf again, if stillbirths and live-births are taken together the total loss of infant life from congenital malformations is greater than the combined figure for mortality from measles, whooping cough, diarrhoea and enteritis. The whole subject bristles with difficulties. On the one hand it represents a genetic problem which certainly needs greater investigation than hitherto. On the other, the startling discovery of the effect of rubella during pregnancy as a factor in the production of congenital cataract and congenital deafness suggests that infection may play a more important part in producing malformations than had previously been thought possible. It points once again to the need for maintaining maternal health and nutrition at the highest possible level during pregnancy.

Infection during the neonatal period undoubtedly causes a greater number of deaths than appears in the table. Certainly it is the lethal factor in many of the prematurely born infants who survive the first few days of life. It must also account for some of the deaths ascribed to atelectasis. The clinical picture of sepsis neonatorum is not always easy to recognize by the inexperienced and throughout all discussions of vital statistics there is the qualifying consideration that few of the certificates issued in the early weeks of life are based upon the results of expert post-mortem examination. It can safely be assumed that infection is more serious than statistics reveal. Yet it is, in fact, now the most hopeful side of the whole picture. For with penicillin and the sulphonamides far more babies can successfully be brought through their infection than ever before. Education must, however, again play a part in showing how infection produces a picture very different from that in older infants and older children, so that early recognition may be made, and early, expert treatment instituted.

This is the broad outline of the problem as we see it to-day in Great Britain. Of the splendid work achieved in this country, of the excellent vital statistics of many of the great cities, of which Chicago is usually quoted to us as a supreme example, and of the good results in infant care in New Zealand, in Holland and elsewhere, I am eager to learn more. What has been possible in the

places with the best figures should be the aim of other centres to attain.

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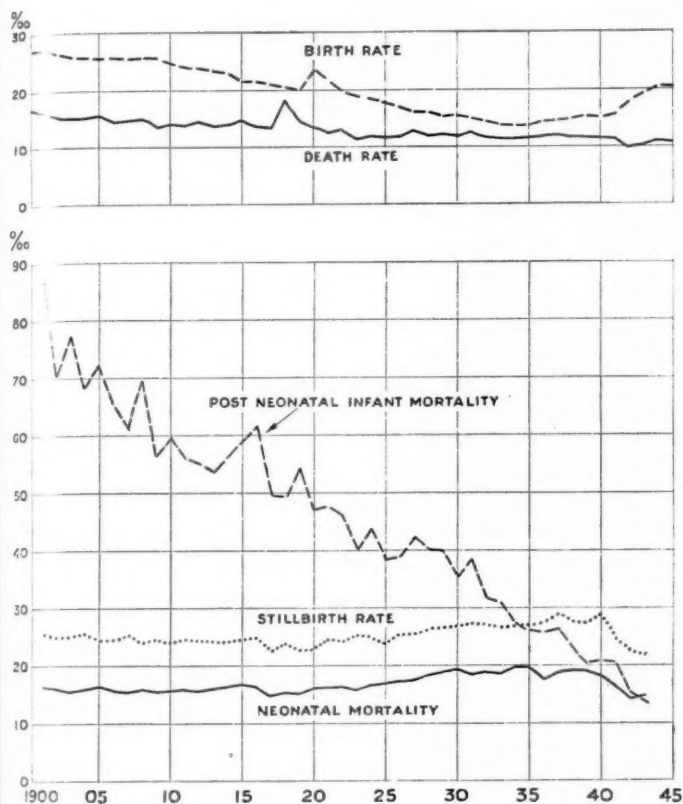
CO-RELATOR.

Neonatal Mortality.

By **Curt Gyllenswärd**, Uppsala, Sweden.

In this paper, the term «neonatal mortality» is applied to deaths occurring during the first week after birth. For the elucidation of the causes of neonatal mortality it is necessary also to study the stillborn. Of these there are two groups to be considered, i.e. infants who die during pregnancy, previous to labour, and those who die during parturition. In the first group death is dependent on internal factors; in the second, in greater or lesser degree on injury inflicted during parturition.

The general mortality rate, calculated per thousand inhabitants, has, except during periods of widespread catastrophe such as war or pandemic influenza, decreased rapidly in all Western countries. This has been the case in Sweden, especially from the end of the 19th century. It decreased from 18.3 per thousand during the period 1871—80 to 11.7 during 1931—40. A considerable part of this decrease must be attributed to the decrease in infant mortality, especially during the first year of life. In Sweden, the mortality rate during the first year of life for live-births has decreased from 10.4 per cent in 1901, to 7.2 per cent in 1911; 6.3 in 1920; 5.4 in 1930; 3.9 in 1940; and at present it is as low as approximately 3 per cent. We observe a similar trend in other countries, although Sweden, Switzerland, Norway, Australia, Holland and New Zealand still show the lowest figures. Against such a background, the number of stillbirths and neonatal deaths comes as a shock. Countries with a low infant mortality rate are



most suitable for a study of these conditions, since the lower the mortality the more frequently are such disturbing factors eliminated, i. e., those which are not directly connected with pregnancy and childbirth. The neonatal mortality rate has increased during recent decades in such countries.

The figure shows a graph of the general death rate, the rate during the first year of birth (with the exception of the first week), neonatal mortality, and stillbirths, as well as the birth-rate curve in Sweden from 1900 to 1943 (1945).

The general mortality rate, as also the infant mortality rate, has decreased practically without interruption. Neonatal mortality and stillbirths, which until 1916 were approximately 15 and 25 respectively per thousand live-births, decreased thereafter during a year or two, later to increase uninterruptedly until about 1940. After a fresh decrease during a year or two, they have since 1942 again increased. The birth-rate decreased considerably until 1934, since when it has risen constantly, at first slowly and then in rapidly increasing tempo.

The minimums of the curves of neonatal mortality and stillbirth are particularly interesting, since they occur during periods of marked scarcity of staples such as food, i. e., in connexion with the crises during World Wars I and II.

The increase in neonatal mortality and stillbirths has not escaped notice, but it has, nevertheless, failed to arouse the attention it deserves. One reason is probably that the considerable decrease in infant mortality has over-shadowed the increase in neonatal mortality. Another reason is perhaps that until now the latter has been ascribed to a relative increase in the number of primiparous births in connexion with the general decrease of the birth-rate. It has usually been considered that these births have a higher rate of mortality than those up to and including the fourth birth. As the birth-rate decreases, the relative number of primiparous births usually increases, and thus the number of neonatal deaths and stillbirths would automatically increase. As the birth-rate increases, this mortality rate would, in consequence, once more decrease. The question would then become a matter of population policy and could be disregarded from the medical standpoint.

It is thus necessary, first of all, to investigate what role is played by primiparity and the displacement in general in the relative birth-parity, in order to determine whether the problem is medical, or belongs to the field of social medicine. We must even now point out that whatever the reason for the increased rate of neonatal mortality and stillbirths, this factor (or these factors), which have such a detrimental effect on the child in the very early stages of life, must have exhausted their injurious effects after the first week of life; or else this effect must thereafter be heavily over-

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compensated by factors working in a favorable direction. The fact that mortality has decreased so considerably during the first year of life — after the first week — whilst neonatal mortality and stillbirths have increased, shows that the infants which are so fragile at, and immediately after, birth have remarkably improved prospects of life now as against formerly, if they survive this first stage. These circumstances point to the conclusion that the cause of the increased rate is to be sought in facts in close connexion with parturition itself. As regards the effect of a larger number of deaths in primiparous deliveries, this also can be explained in the same way, i. e., on the assumption that primiparity is more dangerous to the child than a higher parity. Furthermore, the stillbirths mentioned show a close connexion with neonatal mortality.

I have found in Sweden, on the basis of material from the 18th and 19th centuries (principally from the countryside) and from the nineteen-thirties (principally from the large towns and from maternity hospitals in Stockholm), that of children born in wedlock the first-born have a somewhat higher rate of stillbirths than second, and especially third, parities. The rate of stillbirth for the fourth-born children is, however, higher than for the first. In the first-mentioned material, the stillbirths were 16.2, 15.1, 13.4 and 18.7 respectively, and for the second, 28.3, 17.7, 17.3 and 31.1 respectively per thousand born for the first, second, third and fourth-born child respectively. For all births — without regard to birth parity — the stillbirths were, for the first series, 19.6, and for the second, 24.1, or higher than for first-born infants alone. This shows that the rate of stillbirth is mostly affected by stillbirths in those with a higher birth-parity than 1—3. It is interesting to note how much higher is the rate of stillbirth in the material from the later period than in that of the earlier. In other countries it is often stated that it is only the fifth, or even the seventh or later parity which has a higher rate of stillbirth than the first. In Sweden the birth-rate fell sharply until 1934. This decrease in the birth-rate has, in particular, resulted in a decrease in the number of children in families, i. e., the births of high parity have disappeared. Thus, for example, births of the fourth or later child constituted 50 per cent of all births in the earlier series of the

material just mentioned, whereas in the later series they constituted only 10 per cent. This development has resulted in a considerable decrease, both absolute and relative, of births with relatively high mortality (para 4 and higher), a relative increase of births with very low mortality (para 3 and 2) as well as a relative increase of births with a medium high mortality (primiparity). Further investigation shows that when the birth rate curve rose once more after 1934, the decrease in large numbers of children in one family still continued, whilst the number of first-born children was relatively stationary, and second and third births increased. In their entirety, first births also increased, as did second and third births. It was found that in Stockholm — during seven of the years investigated in the period 1930—1942 — the 33 per cent increase of the total number of children was due to the fact that additional children were born in families in which there was previously only one child. At the same time, the number of childless marriages decreased, in that at least one child was born in such families. Taken together, the displacement in the order of parity had a decreasing effect on mortality, and this was the case in the entire country.

This development has also caused a decrease in the average maternal age. The rate of stillbirth in younger mothers is considerably lower than in those who are older. Between 1934 and 1937, in Sweden, for children born in wedlock, the rate of stillbirth for mothers between 15 and 20 years of age was 1.5 %; 20—25, 1.7 %; 25—30, 2.2 %; 30—35, 3.0 %; 35—40, 3.7 %, and 40—45, 4.8 %. For children born out of wedlock, the rate of stillbirth for mothers between 15—20 years of age was 2.3 %, and for the following age groups, 2.7 %, 3.4 %, 4.2 %, 5.5 % and 6.4 % respectively. Thus we see that the rate of stillbirth rises in proportion to the maternal age. Whilst the married mothers in the 20—25 year group had a stillbirth rate of 1.7 %, the rate was 3.0 % in the 30—35 year group, or nearly double. A comparison between married and unmarried mothers is interesting. The number of stillbirths in the latter category was, in all age groups, approximately 50 % higher than in the former category in the same age groups. An increase of 10 years in the maternal age gives the same deteriora-

tion in the chances of live birth as the difference between the births in and out of wedlock. If, further, we compare the rate of stillbirths in all children born in and out of wedlock in Sweden, irrespective of maternal age, the figure for the latter group between 1921 and 1940 was less than 20 %, and between 1931 and 1940, only 12 % higher. Furthermore, 80 % of all children born out of wedlock are first-born. Children with a higher birth parity are thus infrequent among children born out of wedlock, and they have, moreover, a lower rate of stillbirth than the first-born. This shows that maternal age is far more important as regards stillbirth than birth parity, irrespective of whether the child is first-born or not. Approximately two-thirds of all children born in Sweden at present have mothers in the 20—35 year group, and statistics show a considerable decrease of the relative number of mothers in the 25—30 year group, with a corresponding increase in the lower ages. Thus, with regard to maternal age, recent trends must have caused a decrease in stillbirths and hereby also in neonatal mortality. In Sweden these are in a proportion of 100:64 for children born in wedlock, and 100:81 for those born out of wedlock.

The relative displacement in the birth parity has, without doubt, influenced the rate of stillbirths and neonatal mortality. However, in Sweden at any rate, the cause of the increased neonatal mortality and stillbirth rates cannot be a relative increase of the number of first-born infants. For this reason the problem impinges quite differently upon the interests of medicine and of social medicine, and measures to combat it lie within both fields.

An important basis for such measures would be a more precise knowledge of the causes of death, and in particular whether death — or the injuries which caused it — occurred before, during, or after parturition. A classification of this kind would be extremely valuable.

As regards the causes of death, the only statistics which afford satisfactory conclusions are those based on autopsy material uniformly selected and examined, and on material covering all forms of maternity care and different social groups. We must also take into consideration the difficulties of demonstrating pathologico-anatomic lesions at this age from such causes of death as,

for example, functional lesions in nerve centers following asphyxia. A survey of the 648 neonatal deaths among 61 180 births in two maternity hospitals in Stockholm during the nineteen-twenties gave only »prematurity» as the cause of death for two-thirds of the premature infants, and »internal hemorrhage» for 50 % of the full-term infant deaths. The next highest frequency for both categories was asphyxia. Wallgren has published a study of all neonatal deaths of children born in Gothenburg from 1935 to 1941. He found, in this material, that the cause of death was stated approximately as follows: prematurity, 47 %; injuries during parturition, 25 %; congenital malformations, 14 %; infections, 8 %, and diseases peculiar to neonati, 5 %. At the same time, however, Wallgren points out that Brodin found that in 1913—1917, for 16.5 per thousand dead in Gothenburg during the first two weeks of life, the cause of death was stated as debilitas congenita. During a five-year period twenty years later, the corresponding mortality rate had decreased to 8.5 per thousand. During the same period, the recognized injuries during parturition increased six-fold, and the congenital malformations increased four-fold. Fanconi, in Zürich, has shown that during every 10-year period between 1900 and 1940, for approximately 250 per thousand of those who died during the first year of life, the cause of death was congenital debility, whereas the injuries during parturition increased from 31 per thousand in 1901—1910, to 105 in 1931—1940, and the congenital malformations increased during the same period from 26 to 47 per thousand.

The possibility must not be overlooked that a true basis may exist for the increase in birth injuries. At present, however, published statistics lead only to the conclusion that prematurity has been accorded very great significance as a cause of death in neonati during the first two weeks after birth and during the whole first year of life. It is possible that the increase in stillbirths and in neonatal mortality must be sought in a relative increase in the number suffering from congenital debility. Certain reasons support this opinion, e. g., the rate both of stillbirths and neonatal mortality amongst premature births is many times that of full-term births. One difficulty is, however, immediately encountered.

viz., that of reconciling such a cause with the fact that mortality during the first year of life has in general consistently decreased. Furthermore, it is well known that the rate of stillbirth is higher in the poorer classes of society than among those financially better situated. Thus, Edin has found that in Stockholm, during the nineteen-twenties, the number of stillbirths in families in which the father's income was lower than 4 000 Swedish crowns per annum was double that of families in which the income exceeded 10 000 crowns. An investigation of the frequency of debility has also shown a marked difference between those in good and those in bad financial positions. In two large maternity hospitals in Stockholm in the nineteen-thirties, 7.2 % of all children born in the public wards weighed less than 2 500 grams, as against 4.1 % of those in private rooms. As we know, a general improvement in the standard of living has taken place, and this should have resulted in a decrease of stillbirths, which have on the contrary increased. However, we must consider the possibility of factors which increase the frequency of congenital debility.

Earlier investigations have been considered to demonstrate that children of mothers working outside their homes have a higher rate of stillbirth than others. An increase could therefore be considered due to the increased employment of women in industry. This should become evident in an increase in the frequency of spontaneous abortions. The statistics are, however, somewhat uncertain on this point, and no proof of such an increase has been demonstrated. The next development should rightly be an increase in the frequency of debility.

An investigation of material from country districts gave figures approximately the same as for those treated in private rooms in Stockholm hospitals. A comparison between those delivered in their homes by midwives and in maternity hospitals in 1921—1939 showed that in the former category — chiefly those living in the countryside and in poorer financial circumstances — only 4 % of the children weighed less than 2 700 grams at birth, as against 6.3 % in the latter category. Considerable migration to the towns has taken place, and women have been absorbed into the industries to an ever increasing extent. The rate of stillbirth and neonatal

mortality is now higher in the towns than in the country, although only up to and including the fourth day of life. This agrees with the fact that infant mortality is now higher in the country than in closely populated areas. This is especially interesting in view of the low frequency of debility, since the mothers in the countryside consist to a great extent of wives of small farmholders and others similarly placed, whose work is hard but of a different kind from the «chain-system» work in factories. It is possible that this «flight from the countryside» has increased the frequency of congenital debility. This has possibly increased somewhat for the whole of Sweden, viz., from 4.5 % in 1921—1930, to 4.8 % in 1931—1939, an increase which is, however, only just statistically significant. An investigation, however, of the weight at birth for children in Sweden shows that it has, on an average, increased — both in comparison with earlier material and during the nineteen-thirties — in satisfactory agreement with the increase in length and weight for children of all ages. A closer analysis of the last mentioned material also makes it clear that it is especially children with a weight at birth of somewhat over the earlier average who have increased in number. The increase which has occurred has thus benefited foeti which, in any case, had satisfactory prospects of development. Neither the frequency of debility, nor — a fact which otherwise might possibly have increased the number of injuries at parturition — the relative number of children who are particularly heavy at birth, has changed to any great degree. Both groups are, on the whole, small; and the changes in the registration of borderline cases between children and miscarriages, which have been made from time to time, therefore are relatively unimportant. If those born in maternity hospitals are investigated separately, we find that the rate of stillbirth has increased, at the same time that the frequency of debility has decreased relatively. Relatively considered, stillbirths have increased most in the countryside, where the number of premature births has remained stationary, both absolutely and relatively. If the increase in stillbirths depended on an increase of the number of premature births, the number of stillborn male children should, moreover, have increased more than that of stillborn female children, since this effect would then already have

been apparent during pregnancy. In general, the number of still-born male children is 20 % higher than that of female children, and the difference is still greater in premature stillbirths. In cases of spontaneous abortion, males exceed females by as much as 50 %. Such a displacement has not, however, occurred.

If, finally, a comparison is made for the whole of Sweden between the uncertain increase in the frequency of debility and neonatal mortality, we find that at most only one-third of the latter increase could be explained by a possible increase in the frequency of congenital debility.

The question of whether the child has died before or during parturition is not always easy to decide, except in cases of extreme maceration. In one maternity hospital in Sweden, the number of stillborn infants who died during pregnancy, in the nineteen-thirties, was double that in another hospital, relative to the total number of births, and the differences for hospitals without specially trained obstetricians can be still greater. In agreement with this difference are the varying percentages stated for cases of maceration in stillbirths. Nevertheless, the relation between the sexes should furnish a clue. If death had occurred previous to parturition, we could expect the male children who are well known to be more fragile to be affected to a greater degree than the females. No displacement has, however, taken place concurrent with the increase in stillbirths and neonatal mortality. Male births are, however, less favorably placed with regard to neonatal mortality than to stillbirth. In the latter case the proportion is 119 males to 100 females, whereas in the former the proportion is 132 males to 100 females. Reports appear to indicate that the cause of the increase in stillbirths must be sought in factors arising during parturition, and that, as regards neonatal mortality, further circumstances arise during the first week of life.

It should also be pointed out that the number of births out of wedlock in Sweden has decreased, a fact which should also have decreased mortality. Not only is the rate of stillbirths higher for children born out of wedlock, but they have — as has previously been mentioned — a relatively higher rate of neonatal mortality.

In addition, the rate of stillbirths has decreased for children born out of wedlock in the cities.

One fact which is most alarming is the increase of the mortality rate for mothers in connexion with childbirth. This must, however, be related to the fact that the causes of the increase in stillbirth and neonatal mortality are to be sought in factors which exert their influence during parturition and in connexion with death in childbirth. The rate of death in childbirth was formerly very low in Sweden, but it has once more increased during recent decades. In 1861—1870 before the aseptic era, the rate was 5.48 per thousand mothers; but in 1901—1910 it had decreased to 2.30. In the next ten-year period it was 2.60; in 1921—1930, 2.82; and in 1931—1940 it had increased to 2.92. This increase has occurred parallel to a transition from delivery in the home to delivery in maternity hospitals. In 1901—1905, only 4 % of all births in Sweden took place in a hospital of some kind; 96 % were delivered in their homes by midwives without the assistance of a doctor, as is usual in Sweden, where for more than a century the country has been divided into midwife districts with specially trained midwives. The corresponding figures for 1916—1920 were 10 %; 1926—1930, 21 %; 1931—1935, 33 %; and 1936—1939, 51 %.

The increased number of deaths in childbirth is the more remarkable since the change to delivery in a hospital allows easier access to medical assistance, and a number of factors which complicate parturition, such as contracted pelvis, albuminuria during parturition, etc., should be decreased by means of the increased facilities for preventive maternity and child care. Statistics exist for urban populations, according to which puerperal fever has not increased, although »other diseases of pregnancy» have. The material does not, however, permit any closer analysis.

It is not, therefore, surprising that a connection has been sought between the increase in maternity care in hospitals and the increase in stillbirths and infant mortality. The situation is, however, extremely complicated. It is natural that mortality rates should be higher for deliveries in hospitals than for home deliveries, since the former can be expected to include a relatively larger number of complicated cases. This cannot, however, explain the

increased mortality for the whole country, since this index should have decreased if the complicated cases received better and earlier treatment. Furthermore, the stillbirths should have decreased in the hospitals in the measure that a greater number of normal cases are received, and in the home when a greater number of complicated cases are hospitalized. On the whole, neither has occurred. Stillbirth and neonatal mortality have increased most amongst those living in the country, where births are taking place in an increasing number in hospitals with no special maternity service. Moreover, stillbirth has increased more than neonatal mortality, even if the latter is proportionately higher.

It is therefore necessary to take many factors into consideration. Large areas of Sweden are thinly populated, and the distances are considerable. From the animal world we know that uneasiness and migration in connexion with parturition have an unfavorable effect on both mother and offspring. Wahlund has demonstrated that the Lapps, who lead a nomadic existence, have a very high stillbirth rate, so great that they even have a greater number of female births amongst the live births than does the resident population. A transition from birth in the home to birth in hospital involves moving, often when labor has already started. It has been demonstrated that women in the country, aside from those living near hospitals and particularly those who are in an isolated place, seek admission to a hospital for parturition, on account of the uncertainty of obtaining help from a midwife. The rate of stillbirths is also higher in hospitals than in the home. We must also consider the question of surgical intervention. Fifty per cent of all the births in hospitals in Sweden take place without access to specially trained obstetricians, and the medical personnel has, moreover, other exacting duties to carry out. In two different services in the same maternity hospital it was found, in a seven-year investigation during the period from 1930 to 1942, that 3.8 % in one service, and 9.2 % in the other, underwent instrumental delivery. The division into high, mid and low forceps deliveries was the same in both services. This means that, in one service, relatively more than twice as many high and mid forceps were applied as in the other. At the same time, the number of cases of

parturition albuminuria was twice as great in the service with fewer forceps deliveries but with patients of a lower economic status. The indications differ considerably even in this specialized clinic. The role of anesthesia should not be overlooked. The importance of infections and the possibility of the transmission of infection — particularly to neonati — has once more come into the foreground in recent bacteriological research. A considerable overcrowding increases the difficulties. In 1942—1943, the occupancy of the maternity clinics in the hospitals was 148 %. The time of hospitalization is consequently too short.

The effect of these varying factors cannot be investigated fully without the cooperation of all those involved: obstetricians, other medical men concerned with maternity care, midwives and pediatricians. Lichtenstein demonstrated in 1931 that the mortality — particularly of premature births — decreased considerably in one maternity hospital in Stockholm following the appointment of consulting pediatricians.

The problem of the causes of the increase in several countries of death in childbirth, stillbirths and neonatal mortality, is extremely complicated, and many aspects are as yet unsolved. The opinion that such questions lie entirely in the field of population policy or sociology has not survived in the face of criticism. There are also — and perhaps principally — medical and social-medical aspects. The situation resembles — both from a scientific and practical standpoint — that when Semmelweis took his pioneering steps towards the fight against puerperal fever, even if — fortunately — both the proportions and the outlook are no longer the same. In Semmelweis's day, bacteria had not yet been discovered. He was obliged to base his theories on an unknown, but nevertheless existing factor.

In practice, our measures must also in many instances be taken without more exact knowledge of the injurious factors which prevail. We must, therefore, aim at making available expert examination and expert advice for every mother during pregnancy — so-called prenatal care. An important step is a visit to the home of the future mother. Financial and other deficiencies should be

made good, and suitable help in the home supplied. Expert help in time for childbirth should be available for every mother, and thereafter help both for herself and her child from persons trained for such work and not overburdened with other work, which may even involve risks to the mother. Specially equipped clinics and specially trained medical men should be situated so that every complicated case — or one in which complications are feared — could be admitted, following examination in the home by a doctor or midwife. Indications for surgical intervention should be controlled from time to time. Financial difficulties should be eliminated so that such help could be given irrespective of the financial situation of the patient and of the distance of her from the clinic. Specialist care should be reserved primarily for those who are really in need of it, and not those who live nearest the clinic. The maternity hospitals or institutions should not be overcrowded, and the time of hospitalization should be sufficient. The care of the infants — particularly those who are premature — should be entrusted to pediatricians.

The ultimate aim of maternity care is that every mother — irrespective of her social position, financial circumstances or place of residence — should be afforded the possibility of giving birth to her child under conditions which are as far as possible similar and, in any event, under conditions which are medically, socially and humanely acceptable both for the mother and for the child.

The task of science is to investigate such problems and to pursue them indefatigably. To this end we need uniformly planned and uniformly executed investigations, covering all forms of maternity care and all social groups — preferably simultaneously in several countries — and in cooperation with research workers trained in obstetrics and pediatrics. Such investigations have been planned in Sweden, but hitherto it has not been possible to realize them.

CO-RELATOR.

Neugeborenensterblichkeit.

Von Prof. A. Reuss, Wien, Austria.

Als wichtigste Todesursachen gelten im Allgemeinen: das intrakranielle Geburtstrauma, die Frühgeburt und die sogenannte *Debilitas vitae*, ein Begriff der durchaus berechtigt ist.

Die dem Fetalalter entsprechende Unreife als solche kann auch bei vollkommen funktionsfähigen Organen infolge ungenügender Steuerung der vegetativen Centren den Tod herbeiführen. Diese Insuffizienz — nachweisbar durch die BlutRedox Reaktion n. Meier—Synek — kann individuell verschieden stark ausgeprägt und unter Umständen so hochgradig sein, dass sie auch bei Kindern welche als lebensfähig imponieren, das Leben gefährdet.

Es gibt Kinder, welche am normalen Ende der Schwangerschaft mit Zeichen der Unreife geboren werden (pathologische Reifungsverzögerung) und solche, welche ohne solche Zeichen, aber untergewichtig zur Welt kommen (pathologische Anwuchsverzögerung, intrauterine Dystrophie). Sie können im gleichen Ausmass gefährdet sein wie die Frühgeborenen und infolge funktioneller Organinsuffizienz zugrunde gehen.

Zu den im wesentlichen vegetativ veranlassten Störungen gehören nicht nur die bekannten Erscheinungen der Frühgeburt (Atem- und Kreislaufstörungen, Cyanoseanfalle, Thermolabilität und Folgezustände), sondern auch die Infektanfälligkeit (septisch-pyaemische Krankheiten, Meningitis purulenta), sowie frühzeitig, auch bei Ernährung mit frischer Muttermilch, auftretende Darmstörungen (Enterocolitiden), welche als Folge insuffizienter Bakterienregulation aufzufassen sind.

Eine besondere Gruppe bilden die auf angiospastischer Grundlage zustandekommenden Zustände, wie Akrodynien, Typus *Epidermolysis bullosa dystrophica*, *Dermatitis exfoliativa* u. dgl.

Von grosser Bedeutung sind die durch den Geburtsschock hervorgerufenen Angiospasmen im Gehirn. Sie spielen beim Tod in der Neugeburtsperiode mindestens eine ebenso wichtige Rolle wie die groben, anatomisch nachweisbaren Verletzungen und Blutungen, welche für und oft nichts anderes sind als der Indikator für das schädigende Trauma.

Die serologischen Forschungsergebnisse der letzten Jahre weisen darauf hin, dass auch Antigen-Antikörper-Reaktionen beim Zustandekommen schwerer, letaler Störungen eine Rolle spielen, deren Bedeutung über den Rahmen des Icterus neonatorum gravis hinausgehen dürfte.

Discussion.

Aleksandra Kurowska, M. D., Senior Assistant of the Children's Clinic of Poznań University. (From the Newborn Ward of the Obstetric and Gynecological Hospital for the Province at Poznań; Director, Prof. T. ZWOLINSKI, M. D.)

The total number of infants born in the Obstetric and Gynecological Clinic of the University of Poznań for the period from June 1, 1946 to April 15, 1947 amounted to 2 607. Of these, 2 522 were live births, 85 stillbirths. Of the 2 522 infants born alive, 302 were born with operative assistance (version extraction, forceps, cesarean section), the rest were delivered spontaneously.

Among 2 522 infants, 113 died in the clinic; of these, 47 were girls and 66, boys. When the number of days of survival is taken into account, we may divide these cases into three groups:

- 1) newborn infants who died within 24 hours.
- 2) newborn infants whose death occurred between their second and seventh day of life.
- 3) a group comprising later deaths in the 2nd, 3rd, and 4th weeks of life.

Among these newborn infants must be distinguished those whose weight at birth was less than 1 kg (2 lbs. 3 ozs.), those whose weight at birth was from 1 kg to 2.5 kg (from 2 lbs. 3 ozs. to 5 lbs. 8 ozs.) and those weighing over 2.5 kg (over 5 lbs. 8 ozs.).

In this group, however, must be taken into account those infants who, although their weight at birth was over 2.5 kg (5 lbs. 8 ozs.) must be considered as prematurely born because of their incomplete term of pregnancy and clinical evidences of immaturity.

These data are presented in the following table:

Birth Weight (grams)	Total number of cases	Death within 24 hours	Death between 2 and 7 days of age	Death before reaching 2, 3 or 4 weeks of age
Less than 1 000.....	22	15	7	0
1 000—2 500.....	249	17	29	21
Over 2 500 { Premature ..	30	0	2	0
{ Full-term ...	2 221	6	9	7

As this table shows, of these 113 deaths 78.95 per cent occurred in infants weighing at birth 2.5 kg (5 lbs. 8 ozs.) or less, and 21.05 per cent in infants weighing over 2.5 kg. Two of these latter cases are premature. This, compared with the total number of 271 infants born alive weighing at birth 2.5 kg or less, will fix the death rate of these cases at 33.29 per cent. Thus, among 249 infants weighing between 1 000 and 2 500 grams at births the death rate was 26.9 per cent.

The causes of death among the newborn infants in our series may be further examined. Among these 113 deceased newborn infants, autopsy was performed in 49 cases. As causes of death should be mentioned:

- 1) Injurious factors which affected the infant in utero (syphilis, febrile diseases before labor and during labor, and other chronic diseases);
- 2) Birth injuries;
- 3) Prematurity and non-viability;
- 4) Intracranial hemorrhages;
- 5) Post-natal infections (e. g., influenza, otitis media, pneumonia);
- 6) Congenital defects;
- 7) Other causes.

Ad 1): Four premature infants who had syphilis as their chief disease died in the first fortnight of age. One newborn infant with birth weight of 2 330 gms., whose mother had jaundice since the 8th month of pregnancy, developed poorly from the first day of his life, recovered from a severe and prolonged jaundice, and died in the second half of the third week of life from bronchiolitis and circulatory failure. From the first day of his life this infant gave the impression of an inadequately developed and injured one. Three cases deserve special mention, infants whose mothers came down with high fever either before delivery, on the day of delivery, or during labor. The first case, a fullterm infant, presented from the very moment of birth the picture of serious illness. Death occurred 37 hours after birth. Post-mortem showed bilateral otitis media, diffuse bronchopneumonia, and degeneration of internal organs. In two other cases autopsy showed sepsis. All these infants were severely ill from the start.

Ad 2): One case of breech extraction, fracture of the femur during delivery, and intracranial hemorrhage; death on the second day of life.

Nineteen cases comprise infants born either in asphyxia or with signs of intracranial hemorrhage. Post-mortem in these cases showed either cerebral or meningeal hemorrhages. In one additional case, in which autopsy showed rupture of the liver and a peritoneal hemorrhage, it was difficult to determine whether the bleeding was caused by labor or by deficiency of vitamin K. In any event, these patients had been treated differently from subsequent ones in whom bleeding appeared later. Five of these infants were born by operative delivery.

In connection with this I should add that, in addition to these 19 cases, bleeding was observed in 6 others, though at a later interval, i. e., between the 3rd and the 12th day of life. In all, intracranial hemorrhage was the cause of death in 25 cases.

Ad 3): Prematurity and non-viability caused death in 56 cases.

Ad 4): Intracranial hemorrhages have already been mentioned in connection with injuries during delivery.

Ad 5): Infectious diseases — e. g., influenza, otitis media, or pneumonia — were found in 16 cases.

In two cases pemphigus of the newborn was the cause of death, in one case death was caused by peritonitis, the starting point of which was an umbilical infection.

Ad 6): Among congenital causes should be mentioned one case of an infant with congenital hernia of the umbilical cord. Death occurred 3 days after operation. In an additional case, dextrocardia with congenital cardiac failure was present.

Ad 7): Of other causes of death we found in two cases bleeding into the suprarenal glands.

Table of Causes of Death in the Neonatal Period.

	Number of Cases
Deaths caused by factors injuring the infant in utero (syphilis, febrile diseases of the mother before labor and on the day of labor, chronic jaundice in the last months of pregnancy, and others)	8
Deaths caused by injuries which occurred during labor (fracture of femur, intracranial hemorrhage)	20
Prematurity and non-viability	56
Intracranial hemorrhage at delivery or appearing later	25
Postnatal infections (otitis media, influenza, pneumonia, peritonitis, pemphigus)	19
Congenital malformations	2
Other causes	2

Doctor **Julio A. Bauzá**, Presidente del Consejo del Niño: *Mortalidad Neonatal en el Uruguay año 1943.*

En la República Oriental del Uruguay, país de 186 000 kilómetros cuadrados de superficie y de una población de 2 300 000 habitantes, la mortalidad neo-natal cuenta solamente a aquellos niños, cuya muerte se ha producido luego de haber respirado. Sin embargo, es indudable que, en un cierto número de casos se registran como nacidos muertos, niños que vivieron horas y hasta días, siendo imposible determinar ni aun siquiera aproximadamente si este hecho acontece con frecuencia.

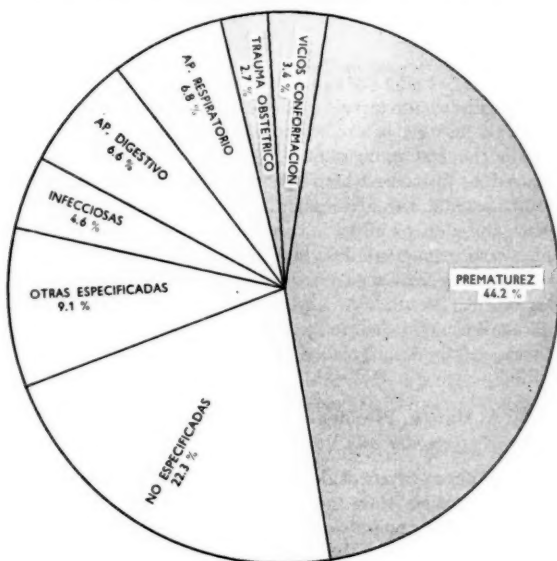
Sólo podría ser posible investigarlo, mediante el servicio de Estadística Vital del Ministerio de Salud Pública, lo que desconocemos que se

pratique. Ello permitiría además, rectificar las cifras de nacido-muertos, que en algunos departamentos del interior del país aparecen exageradamente elevadas.

Estudiando la Mortalidad infantil del año 1943, el último del cual tenemos datos oficiales, encontramos que se produjeron en la República 1079 defunciones de niños menores de un mes, y de ellos 618 en la primera semana, que aparece así como la que ofrece el máximo de peligro para el recién nacido.

Habiéndose registrado en ese año 3387 defunciones de menos de 12 meses, el índice de mortalidad para el primer mes de vida en relación al total de 12 meses es de 32 %. El índice de mortalidad infantil para dicho año 1943, fué de 78 por 1000 nacidos vivos, correspondiendo 24.8 a los menores de un mes. Uruguay registra las cifras más serias de M. I. en la América Latina.

El estudio de las causas más importantes de la mortalidad en el primer mes de la vida del niño, nos muestra los datos siguientes:



Esta clasificación ha sido hecha de acuerdo con los datos del Registro del Estado Civil.

Llamará la atención el número muy alto de enfermedades no especificadas que intervienen en una proporción de más de 20 %, no siendo

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aventurado afirmar, teniendo en cuenta que por lo menos la mitad del número de causas no especificadas corresponden a prematuridad, que esta sola causa es responsable de más de la mitad de la mortalidad del primer mes y que si agregamos los que se deben al trauma obstétrico, se llega fácilmente a 60 % de muertes respondiendo a causas de origen natal y prenatal — en el primer mes de la vida del niño, hecho que habrá de permitirnos abordar luego la profilaxis a ser aplicada.

Esta cifra confirma los resultados a que llegamos en el trabajo que sobre Mortalidad Infantil en el Uruguay, presentamos a la segunda Convención Médica Nacional, celebrada en Montevideo en 1943.

Pasado el primer mes, con 1 079 decesos, en los 3 meses siguientes las cifras se mantienen alrededor de 300, para bajar rápidamente después del 6º mes, hasta los dos últimos meses con las cifras más bajas de poco más de 80 defunciones.

El estudio comparativo de los años 1941, 42 y 43, pone de manifiesto que la proporción de mortalidad neo-natal, por 100 fallecidos de menos de un año, se mantiene entre 31 y 32 por 100, es decir que el descenso observado en la mortalidad infantil, observado en el Uruguay, ha ocurrido con cierto paralelismo en el primer mes y en los 11 meses restantes de la vida.

Profilaxis.

No cabe duda de que la profilaxis de la alta mortalidad neo-natal que se observa entre nosotros, responde a una insuficiente organización de la asistencia del niño en el período pre- y post natal. — La asistencia prenatal de la mujer embarazada en las policlínicas obstétricas, es totalmente insuficiente en la clase pobre, en la cual no existe todavía el hábito de la asistencia prenatal. — Puede decirse que ella se circunscribe sólo a la Ciudad de Montevideo, que cuenta con seis u ocho policlínicas obstétricas. —

En la Campaña, se dispone de comedores para gestantes, madres nodrizas y pre-escolares en gran número en todo el país, habiéndose creado recursos especiales para atenderlos, pero la vigilancia médica es insuficiente en la Capital y en el interior del país.

En compensación de este defecto debemos hacer mención del Artº 37 del Código del Niño que establece la obligatoriedad del descanso un mes antes y otro mes después del parto, con prohibición de despido y pago del 50 % del jornal para toda mujer que trabaja.

Otro medio de profilaxis, a los efectos de la protección del prematuro, es la declaración obligatoria ante la División Primera Infancia del Consejo del Niño de todo recién nacido cuyo peso no exceda a 2 500 gramos; — esta resolución dictada por iniciativa mía en 1938, complementada por la organización de un servicio de Asistencia Externa e Interna, en favor de los prematuros de familias de escasos recursos, está dando

excelentes resultados en la Ciudad de Montevideo, pudiendo afirmarse que se declaran no menos del 70 % de los niños de ese grupo.

Este Servicio que cuenta con una instalación especial, que inmediatamente será ampliada mediante la nueva construcción en la que se invertirá la suma de \$ 100 000.00 aproximadamente, está destinada a tener una gran influencia en la mortalidad neo-natal, permitiendo salvar numerosas vidas que hoy se pierden.

Como complemento de este Servicio que organizamos en la Casa del Niño de Montevideo, se dispone de una Sección de préstamo de incubadoras y camas especiales, con vigilancia a domicilio por nurses especializadas y de una Sección de Lactario para el suministro de leche materna gratis en los casos de verdadera necesidad.

Tales son los medios que se aplican en la Capital del Uruguay para reducir la mortalidad neo-natal, por intermedio del Consejo del Niño, a cuyo esfuerzo se suma el que realiza el Ministerio de Salud Pública en los Servicios de Maternidad de sus distintas dependencias.

Professeur A. Tour, membre-correspondant de l'Académie de Sciences médicales de l'URSS: *La lutte contre la mortalité des nouveau-nés.*

Une des questions les plus ardues de la pédiatrie pratique — question, qui est loin d'être résolue définitivement — est celle des mesures à prendre pour assurer la réduction progressive de la mortalité des nouveau-nés.

L'analyse des causes de la mort des enfants au-dessous de 1 mois a montré qu'à cet âge les enfants meurent surtout de maladies néonatales en second lieu vient la pneumonie. L'importance des troubles aigus de la digestion étant bien moindre et celle des maladies infectieuses presque négligeable.

Afin de réduire la mortalité des enfants pendant le premier mois de leur vie il s'agit non seulement d'obtenir une baisse de la fréquence des maladies à cet âge, mais aussi d'en diminuer la léthalité.

C'est surtout la première semaine après la naissance, c'est à-dire la période du séjour des nouveau-nés à la maternité, qui exige la plus grande attention.

Selon nos données, chez 50 p. 100 des nouveau-nés morts durant les premiers 8—9 jours de leur vie, la cause principale de la mort est la *pneumonie et l'atélectase des poumons*.

Ni les données théoriques, ni les données cliniques ne permettent de considérer la grande fréquence des pneumonies et la haute léthalité de celles-ci chez les nouveau-nés comme dues principalement à une prédisposition anatomo-physiologique des tout jeunes enfants aux maladies des voies respiratoires, à l'absence chez eux de la défense immuno-biologique et à leur non-réactivité contre les divers virus de la pneumonie. Ce sont des facteurs exogènes, dus à la manière dont les enfants sont

soignés, plutôt que les facteurs endogènes particuliers à cet âge, qui sont ici en cause.

Cliniquement, ce sont les bronchopneumonies qui entrent surtout en cause : les pneumonies congénitales et intersticielles sont beaucoup plus rares. La pathogénie et la clinique de ces maladies présentent un grand intérêt, mais dans la pratique elles sont à peu près négligeables.

Afin d'assurer les progrès de la prophylaxie des pneumonies acquises chez les nouveau-nés, il faut :

1. Réduire au minimum le traumatisme pendant l'enfantement et veiller à prévenir l'aspiration par l'enfant des eaux et de la sécrétion des voies génitales de la mère, les traumatismes, surtout ceux du crâne, et l'aspiration pendant et après l'enfantement jouant un rôle important dans la pathogénie des pneumonies chez les nouveau-nés.

2. Assurer aux nouveau-nés les meilleurs soins et la surveillance minutieuse, qu'exige leur état et leur physiologie. On doit surtout veiller à éviter le moindre refroidissement, ainsi que l'aspiration, surtout par les enfants faibles, de lait et d'eau pendant l'alimentation ou durant une éruption accidentelle, et enfin les hypostases et les atelectases pulmonaires.

3. Prévenir l'infection par pneumocoques ou autres coques, et la transmission de la contagion soit par le personnel de l'établissement, soit par les autres enfants.

A ces fins, toute personne présentant les plus légers symptômes de grippe, même sans température élevée, d'angine, de processus purulents etc. ne doit pas être admise à soigner les nouveau-nés. L'observation la plus stricte des règles aseptiques, la prompt constatation des maladies et l'isolation immédiate des enfants malades ou nés de mères malades sont de rigueur.

Afin de diminuer le nombre des morts causées par la pneumonie chez les nouveau-nés, un diagnostic prompt de cette maladie s'impose; un traitement combiné approprié (sulfamides, pénicilline, oxygène, acide ascorbique, transfusion de sang, injection de glucose etc.) doit être institué de bonne heure. Nous avons réussi à réduire à 20—24 p. 100 le chiffre de la mortalité due aux pneumonies chez les nouveau-nés venus à terme et avant terme, mais nous sommes certains de pouvoir à le réduire encore davantage.

Il est certain que le nombre des cas de pneumonie et des morts qui s'en suivent diminuera à mesure que diminueront les enfantements avant terme.

Après les pneumonies, ce sont les hémorragies — et surtout les hémorragies intracrâniennes — qui constitue la cause la plus fréquente des morts néo-natales (25 p. 100).

Bien qu'il soit établi à l'heure actuelle que la tendance aux hémorragies chez les nouveau-nés, et surtout chez ceux qui sont venus avant

terme, est due à cet âge, on n'est guère fondé à y voir la cause essentielle de ces accidents.

On doit tendre à réduire au minimum les traumatismes des nouveau-nés non seulement au cours des enfantements pathologiques, mais aussi au cours des enfantements normaux. La vitamine K doit être prescrite toutes les fois qu'il est nécessaire, et comme agent prophylactique.

C'est au «manque de vitalité» que revient la troisième place parmi les maladies mortelles des nouveau-nés. Notre expérience au service pour nouveau-nés et à la clinique pour enfants nés avant terme à l'Institut pour médecins pédiatres à Leningrade nous permet d'affirmer que dans la grande majorité des cas ce n'est pas le manque de vitalité du au développement incomplet morphologique et fonctionnel (ce qui, certes, a lieu quelquefois) chez les enfants nés avant terme qui est la cause de leur mort, mais bien le manque de soins intelligents, d'alimentation appropriée et de traitement adéquat. Dans notre clinique pour enfants venus avant terme ou nous admettons pour la plupart des enfants dont le poids à la naissance ne dépasse pas deux kilogrammes, et fort souvent atteints de pneumonie ou d'une autre maladie acquise après naissance, la mortalité globale ne revient qu'à 16—20 p. 100, tandis que chez les enfants venus avant terme mais autrement sains elle ne constitue que 8—10 p. 100. Pour les enfants venus avant terme il existe, dans nos maternités, des salles à part, et dans les grandes villes — des cliniques spéciales, où les enfants séjournent pendant 2, 3 ou 4 mois.

Dans nos maternités (la septicémie) n'est pas une cause fréquente de mort des nouveau-nés. La prophylaxie en est bien connue et les sulfamides et surtout la pénicilline donnent d'excellents résultats thérapeutiques.

Nous avons pu observer chez les nouveau-nés des poussées de la maladie que les Américains ont été les premiers à décrire et qu'ils ont nommée «diarrhée épidémique des nouveau-nés». Quant à nous nous la désignons comme «Toxicose septique des nouveau-nés» et l'étude que nous en avons faite nous porte à croire qu'il s'agit ici surtout d'une septicémie intestinale chez les enfants dont la barrière intestinale a été détruite pour une raison ou une autre.

Nous sommes à même d'affirmer que le nombre des maladies et des morts des nouveau-nés peut être réduit dans une mesure considérable. Dans notre service pour nouveau-nés près la clinique de maternité à l'Institut pour médecins pédiatres à Leningrade, le chiffre global des morts des nouveau-nés varie, selon les trimestres, de 0.7 p. 100 à 1.9 p. 100, pour l'année entière constituant environ 1.5 p. 100, et celles des enfants venus à terme — de 0.5 p. 100 à 0.7 p. 100.

Ces chiffres doivent être réduits encore davantage. La protection par l'Etat des enfants pendant la période anté-natale et post-natale, celle accordée aux femmes et surtout aux mères, l'amélioration constante des conditions de la vie et la montée du niveau culturel du peuple — telles en sont les garanties.

Section 1—Factors in Pregnancy Affecting the Child.

Maternal Rubella as a Cause of Congenital Defects in Infancy.

By Lorimer Dods.

Royal Alexander Hospital for Children, Sydney, Australia.

In a recent review of Rubella, Wesselhoeft quoted Shakespeare's «foul fiend» who «gives the web and the pin, squints the eye and makes the harelip». This is the foul fiend Flibbertigibbet: he begins at curfew and walks till the first cock; he gives the webb and the pin, squints the eye and makes the harelip.¹ Dr. Warkany and Dr. Ingalls, whose stimulating and significant exhibits you have all seen, have commenced the unmasking of these «foul fiends» and investigations, which had their beginnings in Australia, have convicted Rubella as one of the causes of congenital defects. The story of the Australian investigations begins with an epidemic of Rubella which Australia experienced during 1940 and the early months of 1941. This epidemic was particularly wide spread, many young adults, including a number of pregnant mothers, were affected and the infection appeared to be more severe than usual. At the height of this epidemic, a short editorial appeared in the Medical Journal of Edinburgh commemorating the centenary of the first description of Rubella to appear in the English language which had been contributed to that journal in the year 1840. This unwitting prologue to Gregg's original paper on Maternal Rubella as a cause of congenital defects emphasised the fact that little had been added to our knowledge of the disease over the past 100 years and that the tendency of the day was to regard Rubella «as a nuisance rather than a

¹ King Lear, Act. 3, Scene 4.

disease». As Aycock and Ingalls have pointed out, this editorial seemed »to set the stage — for events to come within the next few months which dramatically removed Rubella from the Limbo of minor exanthemata», and which denied the impression that it was »a nuisance rather than a disease». Early in 1941 Gregg, an Australian ophthalmic surgeon, recognised the fact that a number of young infants were suffering from an atypical form of congenital cataract. These cataracts, which did not conform to any of the classical types, were usually bi-lateral but sometimes unilateral and were occasionally associated with microphthalmia. Gregg was impressed by the constant involvement of the central nuclear fibres of the lens and felt that this and other features suggested the effect of some noxious factor acting early in pregnancy. Within a few months, he observed 20 infants suffering from congenital cataracts of this type and, by careful questioning discovered that more than 80 % of their mothers gave a history of Rubella during the early months of their pregnancies. Stimulated by this evidence, Gregg communicated with his ophthalmic colleagues in various parts of Australia and was able to collect records of a further group of 58 infants suffering from similar eye defects and to establish the fact that the great majority of their mothers had suffered from Rubella during the early months of their pregnancies. A review of this group of 78 infants showed that the majority were undernourished and that 44 of them presented evidence suggesting congenital cardiac defects. (See Table 1.)

TABLE 1. Infants suffering from atypical congenital cataracts.
(GREGG 1941)

No. of Cases	Cataracts		Congenital Cardiac defects	Microphthalmia
	Double	Single		
78	62	16	44	10

Swan, of South Australia, was impressed by the significance of Gregg's observations and immediately instituted a wide survey of the problem in his own state. This survey, like Gregg's

was based on retrospective questioning of mothers whose infants had suffered from congenital defects of the type described. Swan and his associates confirmed Gregg's original findings and defined other sequelae such as, deaf-mutism of variable degrees, congenital heart disease associated with deaf mutism or occurring alone, mild degrees of microcephaly, dental defects and some mental retardation.

From their survey, Swan and his associates concluded that, when a woman contracts Rubella within the first two months of pregnancy — the chances of her giving birth to a congenitally defective child are in the region of 100 % and, if she contracts it in the third month about 50 %. In comparison with American estimates these figures are very high; possibly further surveys will produce lower estimates.

Later this same group of investigators carried out an inquiry of the prospective type which took the form of a «follow up» study of a group of mothers who had suffered from Rubella during the early months of their pregnancies. This study confirmed, with some minor reservations, Swan's original conclusions and suggested that infants were very rarely affected, if the Rubella occurred after the 4th month of pregnancy. (See Table 2.)

TABLE 2. Relationship between time of contraction of Rubella during pregnancy and the occurrence of congenital malformations in infants born subsequently.
(SWAN 1944.)

Month of Pregnancy	No. of infants with congenital defects	No. of normal children	Total
0-1	4	—	4
1-2	19	1	20
2-3	8	—	8
3-4	2	1	3
4-5	1	—	1
5-6	1	1	2
6-7	—	—	0
7-8	1	—	1
			39

After a careful analysis of the history and symptomatology of the infection which occurred during the pregnancies of these mothers, Swan stated that «clinically we have little doubt that this exanthematous disease — was German Measles», but admitted that conclusive proof, such as the isolation of an appropriate virus was not available. No correlation between the apparent intensity of the maternal infection and the nature of the damage to the infant was noted.

A recent review by Sir Leonard Parsons in the British Medical Bulletin includes a tabulated report of a further 130 cases of congenital defects, following maternal Rubella, which were collected by Gregg during 1944. (See Table 3.)

TABLE 3. Distribution of congenital defects following maternal Rubella in a group of 130 infants collected by Gregg during 1944.

Cases	Deaf-Mutism	Cardiac Defects	Eye Defects
85		—	—
17			—
5	—		—
6	—	—	
8	—		
8			
1		—	

This report of a large series of cases, following another epidemic of Rubella and collected 3 years after Gregg's original series, seems particularly significant.

Probable relationship between the types of congenital defects and the stages of pregnancy at which Rubella occurred.

Although it is difficult to produce accurate figures, the available evidence seems to support the conclusion that the nature of the congenital defects bears some relation to the stage of pregnancy at which the mother contracted Rubella. As Swan and others have pointed out, unless the date of the onset of the last menstrual period and the date of appearance of the rash are known, any attempted estimation of the precise period of preg-

It has been suggested that embryonic tissues are much more susceptible to the effects of infection than adult tissues and that they are most susceptible during the stages of active cell division. In support of this statement, Mann and others have emphasised the parallelism between the stages of pregnancy at which the mothers suffered from Rubella, the expected times of active cell division of the lenticular and cochlear anlagen and the congenital defects found in the infants.

TABLE 4. Approximate relationship between congenital defects and stages of pregnancy at which Rubella occurred.

		Cataract									
							Deafness				
		Cardiac Defects									
Weeks of Pregnancy	5	6	7	8	9	10	11				

the development of cardiac defects is thought to occur between the 5th and the 9th week of intra-uterine life, when the cardiac septa are forming and torsion of the great vessels is taking place.

Reference to Table 4 may help us to appreciate the possible embryological significance of the following clinical observations:

- 1) Infants are rarely affected, if the maternal Rubella occurs after the 12th week of pregnancy.
- 2) If the maternal Rubella occurs after the 8th or 9th week of pregnancy, eye defects are unlikely to develop.
- 3) A combination of eye defects and deaf mutism is relatively uncommon. There were only 9 examples of this combination in the last 130 cases reviewed by Gregg.
- 4) In Gregg's last series of 130 cases, congenital cardiac defects were more than four times as common in the infants suffering from cataracts as in those suffering from deafness without eye defects.

Prevention: —

Various suggestions have been made about preventing or treating Rubella during the early months of pregnancy but, as Sir Leonard Parsons has wisely pointed out, »There is one obvious, practical drawback to any method of prevention or treatment, namely that the ill-effects of Rubella are produced in the early weeks of pregnancy and the mother may well be exposed or develop the disease before she realises that she is pregnant.

At present, deliberate exposure of all girls to Rubella at some time before puberty would seem to be one practical approach to this problem.

In conclusion, may I emphasize the fact that I have not taken any active part in the investigation of this problem and thank you for allowing me to say something about the work of my countrymen in this field.

The Effect of Prenatal Nutrition on the Mother and Child.

By **J. Harry Ebbs, M. D.**

Toronto, Canada.

A preliminary report of the result of improving the prenatal diet of a group of mothers was reported in 1941 (1). Unfortunately, this study was terminated by the effects of the war. A summary of the cases recorded up to that time, are presented in the following slides:

It was found that the most satisfactory method of determining the individual woman's diet, was to have a record kept of everything consumed for each meal during a period of one week. This record was analysed by a dietitian attached to the clinic, as soon after the woman had registered at the clinic as possible. This diet check was repeated at a later date.

We selected those for study, who had a poor diet record and a low income and who had not reached the end of the sixth month of their pregnancy. In other words, they had at least three months for prenatal observation. Alternate patients were left on their poor diets; the other patients in this group with a poor diet and low income, were given certain foods which improved their diet to a fairly good one; these are referred to as the «supplemented diet group». The extra foods were given until six week's after delivery; these foods consisted of milk 30 ounces daily; egg, one daily; canned tomatoes 32 ounces weekly; cheese one-half pound weekly; oranges seven per week; Viosterol capsules containing

TABLE I.

Average daily calories:

	Control	Supplemented
1st record	1.672	1.690
2nd record	1.837	2.424

Average daily protein:

1st record	56	56
2nd record	62	94

Average daily calcium:

1st record	0.537	0.562
2nd record	0.746	1.61

two thousand units of Vitamin D, one daily; a palatable form of wheat germ, two tablespoonfuls daily. Instructions were also given for planning the remainder of the diet on the available income. Analysis of the diet record showed the low intake in the initial diet list with considerable improvement in the supplemented group after the extra foods were started.

In a number of cases, the foods were actually checked and weighed in the home, indicating that there was a reasonably accurate record being kept by the mothers.

TABLE II. Past history.

	Control	Supplemented
Primipara	26	26
No major complications	34	33
Stillborn	8	1
Miscarriage	30	26
Premature	8	11
Toxemia	2	6

The average duration of prenatal observation was about four and a half months; the number of primipara in each group, was also the same; the large number of miscarriages, stillbirths, premature births and toxæmia of pregnancy was high in these women; 50 % of those who had had previous pregnancies had had major complications; in some cases, many had occurred with the same patient. The Obstetricians and nurses in charge of the patients, were not aware of the diet group to which the patient belonged; any patient found to have any complicating condition at the onset was excluded. The Senior Resident Obstetrician in charge of the patient in the prenatal clinic and in the hospital, gave his rating of the condition and progress of the patient for each period of pregnancy. The complications which he has listed, are shown in the following slides.

TABLE III. Prenatal period.

	Control	Supplemented
Numerous complaints	24	14
Anemia	24	15
Toxaemia	13	9
Hemorrhage	10	6
Pyelitis	5	3
Severe vomiting	1	1

In the prenatal period, it is noted that numerous minor complaints were recorded frequently. These included pains and aches, and other disturbances, such as anemia, various grades of toxæmia, hemorrhage which included any prenatal vaginal bleeding, severe vomiting and infection. The figures in this table and in the following tables, give no indication of the general condition of these women attending the clinic. The difference after a short period on the supplemented diet, was so striking that those in attendance in clinic, often remarked at the change which had taken place in the general attitude and bearing of these women. Their outlook on the pregnancy itself, the absence of their minor complaints, their interest in life and what was going on, was most remarkable and to me was one of the most outstanding features of this study.

TABLE IV. Labour.

	Control	Supplemented
Prolonged, difficult.....	16	5
Hemorrhage	10	9
Premature.....	5	2
Miscarriage	4	1
Stillborn	3	1

This was further emphasized during labour, when prolonged labour was much less frequent in those who received the supplemented diet. Many of them offered the remark that they had never had such an easy labour; certainly their general condition and the way in which they stood the actual process of delivery, the absence of tiring and so on, was markedly different in the two groups; the higher incidence of miscarriages in the control group is questionable, since many of the patients did not come under observation until the sixth month of pregnancy, when the period for miscarriage was gone.

TABLE V. Convalescence in hospital.

	Control	Supplemented
Anaemia	23	11
Fever	11	10
Pelvic inflammation.....	9	3
Breast inflammation	5	2
Phlebitis	2	1
Hemorrhage	1	0

TABLE VI. Six weeks after delivery.

	Control	Supplemented
Numerous complaints	7	4
Anaemia	8	0
Hemorrhage	3	1
Cervicitis, vaginitis	5	1
Miscellaneous	6	4

Anemia is listed as those with a hemoglobin below 65 %. The average amount of hemoglobin at the time of delivery was higher in the supplemented group. Ascorbic Acid levels were also higher. Again in the baby, the difficulty of using any reliable yardstick, was apparent.

TABLE VII. Condition of baby.

	Control	Supplemented
Prematurity	5	1
Miscarriage	4	1 (G. C.)
Stillborn	3	1 (Anencephalic)
Slow progress	16	4
Fever	2	1
Difficult resuscitation	2	0
Convulsions	1	0
Died in hospital	1	1 (Mongol with spina bifida)
Skin infection	0	1

However, the appearance of the infant in the two groups was so different that it was possible to determine with reasonable accuracy the group to which the mother belonged by looking at the infant.

TABLE VIII. Feeding.

	Control	Supplemented
Breast at 2 weeks	91 %	93 %
Artificial at 2 weeks	9 %	7 %
Breast at 6 weeks	53 %	78 %
Artificial at 6 weeks	47 %	22 %

The difference in ability to nurse the baby at the breast is shown rather strikingly since more of the mothers who received the supplemented diet, continued to nurse their baby after they left the hospital. There was however, a decided drop in the incidence after the diet had been stopped at six weeks after delivery.

A follow-up of these babies had been planned and was attempted but unfortunately could not be completed. A prelimi-

nary group which were brought back for re-check indicated that there had been a higher incidence of difficulties, including failure to thrive, severe infections, tetany, etc., in those in the control group as compared with those in the supplemented diet group.

The Obstetrician's final rating of the mother and infant and the whole course of pregnancy, showed that more than twice as many of the pregnancies in the supplemented diet group, were classed as «excellent», as compared with those in the control group. This rating, does not however, indicate the frequency with which we noted improvement in the general mental attitude of patients in the supplemented diet group, nor does it indicate the number who lost their minor aches and pains and numerous complaints even after delivery. These were factors which could not be accurately measured.

In order to appreciate the differences in this study, compared with others which have been reported in recent years, it would be as well to investigate the background of the patients attending our clinic. The outstanding features were the large number of women, over 40 %, whose families were on Welfare Relief; also a large number who had had previous serious complications of pregnancy. This being the clinic attached to the teaching department of the University, it was only natural that many of the patients attending, were doing so because of previous complications. Those families not on relief, were on a pitifully low income; the average being two dollars and sixty-five cents (\$2.65) per week, per person. Many of these families have been living under these conditions for several years, as we were experiencing during that time, a period of economic depression, which was later relieved by the war conditions.

As Doctor Clement Smith (2) has pointed out, as a result of his observation on Maternal Under-nutrition in Holland, one must be very careful not to attribute all of the changes to Nutrition. One has the very definite feeling that the length of time that maternal malnutrition has been in existence, is of great importance. Another factor is one which has been brought out by this study and that is that previous complications, abnormalities, of one kind or another, also are important. The work of Dr. Warkany (3)

indicates that the inherited congenital abnormalities may also be of importance.

Burke and Company workers, have shown the relation between the condition of the off-spring and the prenatal nutritional intake of the mother.

Antonov (5) has reported the results of the severe hunger on mothers and their off-spring during the siege of Leningrad. The incidence of stillbirths and premature births was much higher. The weight of newborn infants was less and their generally lowered vitality was accompanied by an increased morbidity in the newborn period.

These and other observations, both in human populations and in well-known animal experiments, indicate that states of marked undernutrition in the mother, will have an influence in the outcome of pregnancy and upon the offspring.

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Notes cliniques sur un cas d'enfant du radium».

Par Maurice Lamy et Melle M. L. Jammet, Paris.

L'enfant qui fait l'objet de cette observation a été soumise à l'action du radium au troisième mois de la vie intra-utérine. Nous avons constaté chez elle un nanisme avec microcéphalie et arriération psycho-motrice.¹ Plus tard, nous avons vu évoluer chez elle une déficience rénale avec rachitisme.²

¹ LAMY (MAURICE), JAMMET (Melle M. L.), POGNAN (Mme C.) et Melle SCHWEISGUTH (Melle O.): Nanisme microcéphalique chez une enfant exposée à l'action du radium au troisième mois de la vie intra-utérine. Bull. et Mém. de la Soc. Méd. des Hôp. de Paris, 59: 35—36, 1943.

² LAMY (MAURICE), JAMMET (Melle M. L.) et PALEY (P. Y.): Nanisme, troubles du fonctionnement rénal et rachitisme, chez une enfant exposée à l'action du radium au troisième mois de la vie intra-utérine. Bull. et Mémoires de la Société Médicale des Hôpitaux de Paris 62: 329—331, 1946.

L'enfant M. Yvonne nous a été amenée pour la première fois à l'âge de 21 mois; son aspect était très particulier; elle était naine, microcéphale, arriérée; sa morphologie très spéciale faisait songer d'emblée au diagnostic d'enfant des rayons».

L'interrogatoire de sa mère permettait en réalité de rattacher ces troubles à l'action d'un traitement curiethérapique pratiqué au 3^{ème} mois de la grossesse.

Madame M. âgée de 41 ans, mère d'un 1^{er} enfant normal, avait consulté, au 3^{ème} mois d'une deuxième grossesse pour des pertes blanches assez abondantes.

On fit alors une biopsie du col utérin et, le diagnostic de cancer du col ayant été porté, on appliqua malgré la connaissance de la grossesse un traitement curiethérapique. On posa 3 tubes au niveau du col; la dose totale fut de 32 millicuries détruits.

L'évolution de la grossesse se poursuivit normalement; l'accouchement survint avant terme, à 8 mois et 1 semaine et fut assez difficile; l'enfant ne pesait que 1 kg 500 gr.

Elle fut nourrie exclusivement au lait jusqu'à 10 mois; à partir de cet âge elle accepta, en outre, quelques bouillies liquides, mais refusa tout aliment solide.

Lorsqu'elle nous fut amenée pour la 1^{ère} fois à l'âge de 21 mois, son hypotrophie, sa morphologie très spéciale, son arriération psycho-motrice étaient extrêmes.

La taille était restée très petite, l'enfant mesurait 70 cms à 21 mois, (taille normale d'un enfant, d'un an) et pesait 5 Kgs 700 (poids d'un enfant de 4 mois 1/2 à 5 mois). Sa tête était demeurée particulièrement petite, son périmètre crânien était de 37 cms, 5 (ce qui correspond au périmètre crânien d'un enfant de 2 mois, le chiffre normal pour 21 mois étant de 48 cms). La microcéphalie était d'ailleurs évidente dès le premier regard jeté sur l'enfant.

Les autres parties du corps semblaient à première vue assez harmonieusement proportionnées, mais cependant les formes n'étaient pas celles d'un bébé de cet âge; les membres étaient longs et grêles, le corps mince et élancé; l'aspect général était celui d'un petit corps d'adulte et non celui d'un corps de bébé; les diverses mensurations qui ont été effectuées corroboraient tout à fait cette première impression générale.

A ce nanisme microcéphalique s'ajoutait une arriération psycho-motrice extrême; l'enfant ne se tenait assise que depuis quelques mois, était incapable de rester debout, même soutenue; elle disait à peine «papa et maman», ne comprenait pas l'ordre même le plus simple, se souillait la nuit et le jour, s'agitait sans cesse, criant, riant aux éclats, se débattant pendant l'examen.

L'examen ophtalmoscopique mettait en évidence une microphthalmie,

un léger nystagmus lié vraisemblablement à une diminution de l'acuité visuelle, enfin une hypermétropie.

L'éruption dentaire était retardée, l'enfant n'avait que 6 dents à 21 mois.

L'examen radiologique de son squelette ne montrait pas de retard dans la date d'apparition des noyaux d'ossification; on avait même l'impression d'une certaine accélération; le point condylien huméral, visible normalement au début de la 3^{ème} année existait déjà; en revanche le point épiphysaire supérieur du péroné (qui apparaît vers l'âge de 2 ans) n'était pas encore visible. Il n'existait à ce moment aucun signe radiologique de rachitisme.

Une ventriculographie enfin montrait des ventricules de forme normale; il n'y avait pas d'hydrocéphalie interne.

Dans les années suivantes, l'enfant nous a été amenée assez régulièrement. Son développement physique et psycho-moteur n'a fait que des progrès très faibles et très lents.

A 3 ans et 9 mois elle était demeurée naine, mesurant 80 cms, pesant 8 kg 100; son corps, ses membres étaient minces et grêles; la microcéphalie, la microphthalmie étaient inchangées, l'arriération psycho-motrice demeurait considérable; l'enfant ne marchait pas seule, construisait à grand peine de courtes phrases de 2 à 3 mots, urinait au lit.

Son alimentation était toujours aussi difficile, elle refusait avec violence toute alimentation solide mais réclamait sans cesse à boire.

A ce moment nous avons été frappés par la pâleur de l'enfant et par les déformations osseuses qu'elle présentait depuis peu.

Les avant-bras, les jambes étaient incurvées en avant et en dedans, les poignets les chevilles étaient tuméfiées par de véritables bourrelets sus-malléolaires; lorsqu'on faisait marcher l'enfant en la soutenant, les 2 pieds — le gauche surtout — se mettaient en varus, il n'y avait pas de modification des côtes ou du squelette crânien. On fit alors le diagnostic de rachitisme qui fut confirmé par l'examen radiographique; les épiphyses de l'extrémité inférieure de l'humérus, des 2 os de l'avant-bras, des 2 os de la jambe, étaient décalcifiées, élargies en cupule, leurs bords étaient flous et comme grignotés.

On institua alors un traitement par l'ergostérol irradié, et en quelques mois on vit disparaître les manifestations radiologiques, s'atténuer puis cesser les manifestations osseuses.

Mais frappés par la pâleur de l'enfant, sa soif vive qui contrastait avec une anorexie insurmontable pour les aliments solides, nous avons étudié le fonctionnement rénal de cette petite fille et nous avons pu constater les signes d'une néphrite chronique azotémique.

L'indocilité, l'agitation de l'enfant rendaient impossible l'évaluation exacte du taux journalier des urines.

Des traces d'albumine furent trouvées à un examen; plusieurs autres

recherches demeurèrent négatives. L'examen bactériologique des urines est demeuré négatif. Les urines étudiées par étalement direct et après centrifugation ne renfermaient ni pus, ni germes. On a trouvé quelques hématies dans le culot de centrifugation, jamais de cylindres granuleux.

L'étude de l'urée sanguine nous a donné des chiffres constamment élevés: 2 gr 70, 2 gr 90 ‰.

Il existait une hypoprotidémie très notable, le taux des protides totaux était de 44 grs, celui de l'albumine de 29 gr, celui de la globuline de 15 gr, le rapport $\frac{A}{G}$ de 1.9.

Le chiffre des lipides totaux était de 7.80, celui du cholestérol de 2 gr 60, des chlorures sanguins de 7 gr 30, du calcium de 0 gr 092, du phosphore de 0 gr 050.

Enfin, il existait une certaine anémie: 3 200 000 hématies, 65 % d'hémoglobine, le chiffre des globules blancs était normal.

La réaction de Bordet-Wassermann était négative dans le sang.

La tension artérielle n'a pu être mesurée chez cette enfant agitée et indocile. Il n'existait pas d'altération du fond d'oeil. Chez cette enfant fragile, dont l'azotémie était élevée nous n'avons pas osé pratiquer d'urographie ou de pyélographie.

Tous les troubles dont a souffert notre petite malade doivent, nous semble-t-il, être rattachés à l'irradiation par le radium qu'elle a subie au 3^{ème} mois de sa vie intra-utérine.

La naissance d'un enfant nain, arriéré, microcéphale, après exposition de l'utérus maternel aux rayons X pendant les 1^{ers} mois de la grossesse est un fait bien connu depuis la première description qu'ont donnée APERT et KERMORGANT¹, en 1923, de «l'enfant des rayons». Connue aussi, bien que plus tardivement, est le même syndrome, lié à l'action du radium. Avant que fussent publiées des observations cliniques la possibilité d'une telle lésion avait été envisagée et réalisée expérimentalement par BOHN et PLATT qui, en 1903, soumettant à l'action du radium les oeufs de différents animaux avaient réalisé des malformations plus ou moins complexes allant jusqu'à l'anophtalmie et l'anencéphalie.

Nous avons retrouvé dans la littérature de multiples observations d'enfants nains, microcéphales, idiots, dont la mère avait subi un traitement curiethérapique sur l'utérus pendant les 3 premiers mois de sa grossesse.

¹ APERT (E.) et KERMORGANT: L'enfant des rayons X. La Presse Médicale, 31: 1020, 1923.

Cependant certains curiethérapeutes ou gynécologues nient cette action et contestent le danger de la curiethérapie au cours de la grossesse. Vital Aza, en 1917 a publié l'observation d'une femme irradiée pendant sa grossesse sans dommage apparent pour le fœtus; d'autres auteurs partagent son opinion, tout en admettant cependant la fréquence des morts «in utéro», des avortements et des accouchements dystociques.

En réalité, la preuve est maintenant faite de l'action nocive du radium sur le fœtus. Cette action semble surtout redoutable dans les 1^{ers} mois de la grossesse, alors que le fœtus encore petit est dangereusement exposé au rayonnement des foyers placés dans les culs-de-sac vaginaux ou dans le col utérin. Le radium n'exerçant son action qu'à courte distance, moins de 4 cms, la croissance du fœtus le mettrait ensuite à l'abri des rayonnements.

Moins connue est l'adjonction au syndrome de troubles qui nous semblent appartenir au tableau du rachitisme rénal.

Les manifestations de défaillance rénale chronique que nous avons observées étaient exactement celles du nanisme rénal.

La polydipsie si intense et si précoce en a été, comme, c'est la règle, le signe révélateur; cette enfant tourmentait sans cesse sa famille pour obtenir à boire, n'acceptait qu'à grand peine une alimentation solide; à 5 ans, son alimentation était encore presque exclusivement liquide.

L'albuminurie, peu importante et transitoire, l'azotémie élevée, l'absence d'altérations vasculaires et d'oedèmes sont aussi des traits habituels de la déficience rénale progressive qui caractérise le nanisme rénal.

Dans ce syndrome complexe, il est naturellement impossible de faire la part de l'insuffisance rénale dans le déterminisme des troubles de la croissance. Sans aucune atteinte rénale «l'enfant des rayons» demeure habituellement nain.

Le rachitisme important qui a frappé l'enfant peut, nous semble-t-il, être comparé aux lésions rachitiques qui s'observaient souvent au cours des lésions rénales chroniques de l'enfance. C'était, comme il est habituel, un rachitisme tardif frappant uniquement les membres, respectant le crâne.

Le taux du calcium et du phosphore sanguin demeuré pratique-

ment normal ne peut constituer un argument pour ou contre l'origine rénale du syndrome osseux.

La guérison rapide du syndrome rachitique par l'emploi de fortes doses d'ergostérol irradié (2 ampoules de 15 milligrammes de vitamines D²) pourrait être considérée comme un argument contre l'origine rénale de ce rachitisme; la majorité des auteurs en effet, considère le rachitisme rénal comme inaccessible à la thérapeutique.

En réalité l'emploi de doses élevées de vitamines D permet chez ces sujets la guérison des troubles osseux comme nous avons pu l'observer de façon évidente chez deux autres petites malades atteints de rachitisme tardif au cours d'une déficience rénale, progressive, avec malformations urinaires et petits reins atrophiques congénitaux.

Nous avons d'ailleurs retrouvé dans la littérature l'observation d'un enfant porteur de la même association morbide que notre petit malade. S. J. GLASS¹ a eu l'occasion de traiter une petite fille examinée antérieurement par Amesse et Black. Ceux-ci avaient porté chez elle le diagnostic de rachitisme rénal, mais n'avaient pas su que la mère de l'enfant avait subi du 3^{ème} au 8^{ème} mois de sa grossesse — en vue d'obtenir un avortement thérapeutique — un traitement par les rayons X. Cette enfant était de très petite taille, mince et élancée. Son crâne était de dimensions très réduites, son arriération psycho-motrice était considérable. Elle était en outre atteinte d'une déficience rénale progressive avec rachitisme. L'enfant ayant succombé à une méningite otitique, l'autopsie montra des reins minuscules avec infection des voies urinaires sans dilatation notable de celles-ci. L'examen histologique montra les lésions rénales habituellement rencontrées au cours du nanisme rénal. On nota, en outre, à l'examen du cerveau, une hypoplasie des cellules nerveuses; il existait en outre une hyperplasie oedémateuse d'une parathyroïde.

S. J. GLASS considère que le rachitisme est lié à la lésion rénale sans pouvoir préciser les liens qui rattachent le syndrome rénal et les lésions nerveuses.

D'autre par, une expérimentation très intéressante réalisée

¹ GLASS (S. J.), *The Journal of clinical endocrinology*, 4: 47, fébr. 1944.

par K. MADDOX¹, dès 1930, prouve que l'action des rayons X sur le rein peut provoquer une néphrite chronique avec nanisme. Chez de jeunes chiots de 6 à 8 semaines, il exposa directement aux rayons l'un des deux reins après l'avoir extériorisé, il remit ensuite le rein en place et pratiqua 10 jours plus tard une néphrectomie du rein opposé.

Sur 31 chiens opérés 14 ont eu une survie assez longue pour pouvoir être utilement observés; l'un d'eux resta nain, 2 autres eurent un retard modéré du développement; chez un autre enfin le retard de croissance initial s'accéléra ultérieurement, chez un des sujets apparut un rachitisme sévère.

Il semble donc prouvé que l'irradiation du rein peut aboutir à une lésion rénale chronique avec troubles du développement et rachitisme.

Résumé.

L'observation ci-dessus concerne une enfant soumise à l'action du radium au troisième mois de la vie intra-utérine. Il existait chez elle, une microcéphalie, une arriération psycho-motrice, un nanisme, un syndrome d'insuffisance rénale avec rachitisme. Le radium a agi, semble-t-il, sur le développement du système nerveux central, mais aussi sur celui des reins.

The Pathogenetic Unity of Icterus Neonatorum Levis and Gravis in the Light of Recent Knowledge Furnished by the Study of Blood-groups.

By **G. Lenart**, Budapest, Hungary.

According to prevailing opinion the «physiologic» jaundice of the newborn and Icterus neonatorum gravis are two phenomena independent of each other and of different origin. As long as 20 years ago I expressed the opinion supported by arguments and proofs that icterus neonatorum levis and gravis (which, from now on, I shall refer to as I. n. l. and I. n. gr.) are but two forms of

¹ MADDOX (K.): Thèse, Sydney, 1930; résumé in the Medical Journal of Australia, April 1932.

various intensity of the hyperbilirubinaemia of newborn infants. In 1928 I ascribed all these phenomena to isoagglutination taking place in the child partly before birth and partly thereafter. On the basis of recent investigations it is generally agreed that I. n. gr. is due to isoagglutination in connection with the Rhesus-factor. However it has not yet been recognized that the same may hold true of I. n. l., due as I stated to ABO-isoagglutination, so that the strict separation of I. n. l. and I. n. gr. may perhaps be warranted from a clinical but not from a pathogenetical viewpoint.

My theory says — and I quote —: »The maternal isoagglutinins enter through the placenta into the fetal circulation. If the fetus happens to be a heterospecific one possessing the additional property of belonging to a group characterized by isoagglutinogens corresponding to the maternal isoagglutinins, isoagglutination and haemolysis will take place. In our opinion fetal hyperbilirubinaemia is first of all a consequence of isoagglutination phenomena.»

There is no space here to go into all the facts, arguments, observations and their statistical evaluation by means of which I could demonstrate the validity of my theory for all kinds of hyperbilirubinaemia except those due to developmental anomalies and refute all possible objections, therefore I only quote the last words of one of my articles published in 1928 as follows: » . . . we are justified in saying that isoagglutination and haemolysis resulting in an enhanced bilirubinemia begin in the intrauterine period. These processes continue after birth and may last up to a fortnight. According to their intensity they will lead to simple hyperbilirubinaemia, icterus neonatorum and very rarely to icterus neonatorum gravis. The extent of the processes will be determined by the proportion of the maternal isoagglutinins to the fetal isoagglutinogens. The various qualitative and quantitative factors which determine this relation (namely agglutinophilia, Bouchet's phenomenon, the circumstances of the delivery, behavior of the colostrum, titre-differences a. s. f.) are responsible for the clinical pattern of the disease, the rich variety of its forms ranging from latent jaundice through I. n. l. to I. n. gr.» So, even at that early time I emphasized that no essential difference exists between I. n. l. and I. n. gr. The general acceptance of the in-

contestable fact that I. n. gr. is due to isoagglutination is, since I have proved the same for I. n. l. equivalent to the general acknowledgement of my thesis. This conclusion has however not yet been drawn by the authors concerned with this problem (perhaps because they were or are not acquainted with the agglutination-theory of I. n. l.).

If recent discoveries concerning the Rh-factor are taken into consideration my theory may be formulated as follows: Icterus neonatorum (both levis and gravis) is a sequel of isoagglutination. As to its course it may be mild or grave; as to the cause of the isoagglutination the jaundice may be an ABO-icterus or a Rh-icterus. It is an interesting but as we shall see not an accidental fact that I. n. l. is a result of ABO-isoagglutination whereas I. n. gr. is mostly due to the Rh-factor. Thus I. n. l. i. e. ABO-icterus and I. n. gr. i. e. Rh-icterus are almost identical — almost but not entirely, as »gravis» cases may be caused by ABO-isoagglutination and conversely there may be »levis» cases due to the Rh-factor.

The difference between the two aspects of I. n. can perhaps be explained by the physical and chemical differences of the ABO- and the Rh-agglutinogens. Since the ABO-antigens are readily dissolved in water, they can be found not only in the erythrocytes and the cells of the parenchymatous organs, but also in the serum and the intercellular fluid. On the other hand the Rh-antigen being alcohol-soluble and only in a very slight measure water-soluble, it may accumulate in or on the cells but can hardly be found in the body-fluid (BOORMAN and DODD). Thus while a considerable quantity of the ABO-antibodies is intercepted by the antigens that are present in the bodyfluids and thus can do but little harm, the Rh-antibodies find their way to the erythrocytes and the cells of the parenchymatous organs unimpeded and so may result in grave anaemia, cirrhosis of the liver, Kernicterus and so on. In the case of an ABO-antibody invasion of the fetal organism the grave sequels are prevented by the antigens contained in the body-fluids of the »Secretors». This is the most obvious explanation of the fact that in the majority of cases an ABO-icterus is an I. n. l., whereas the Rh-icterus is an I. n. gr.

As every new theory devised for the explanation of natural

phenomena, ours too must fulfill two essential conditions before it can claim universal acceptance: 1) it must disprove the theory held valid until then, 2) it must offer a satisfactory explanation of *all* known facts.

The first postulate can readily be met. From among the numerous theories bearing on the pathogenesis of the so-called physiologic jaundice (nearly all of which consider the I. n. gr. a separate condition not to be treated in that connection) only one teleological theorem survived. It says that after birth when oxygen is abundantly supplied a considerable part of the bloodcorpuscles which were necessary during the oxygen-shortage of intrauterine life becomes superfluous. These corpuscles are destroyed and the excess quantity of bilirubin released leads to jaundice. This theory cannot answer several questions of paramount importance. What is the mechanism destroying the erythrocyte-surplus in a few days? As demonstrated by many cases of incompatible blood transfusions it is impossible that the mechanism generally observed in extrauterine life should be operating so rapidly. How then can it be explained that in premature birth the newborn show intensive symptoms of jaundice some hours after delivery? How can hyperbilirubinaemia which is present in every infant at that time of life be attributed to an erythrocyte destruction beginning only after delivery? A further difficulty: oxygen-shortage is an essential feature of *all* pregnancies. Thus physiologic jaundice should occur in all newborn. Yet it is absent in about 40 to 50 % of all cases.

Evidently the polyglobulia and the consequent oxygen-surplus of the newborn does not explain the origin of I. n. satisfactorily. The last mentioned objection, i. e. the problem of the percentage of the jaundice, must nevertheless be faced also by the isoagglutination theory with regard to both ABO- and Rh-icterus.

From the point of view of the ABO-system 35 % of all pregnancies are agglutinophile. Should only these pregnancies lead to I. n. I., only 35 out of 100 newborn would have jaundice instead of the 50 to 60 actually observed. The constellation: Rh-negative mother/Rh-positive fetus, that is to say the combination promoting isoagglutination in the fetus, is realized in about 12 % of all

pregnancies, whereas haemolytic disease of the newborn (to be referred to as M. h. n.) is observed in only 0.3 to 0.4 % of all pregnancies. Besides, about one tenth of the M. h. n. cases originate in a mother/fetus relation other than Rh-negative/Rh-positive.

The deviation of the number of cases expected on the basis of calculation from those observed is explained as follows:

1) The placenta is not always permeable to the maternal agglutinins.

2) The mother is capable of antibody-production but peristatic causes prevent it.

3) The mother is incapable to produce anti-Rh agglutinins owing to the inhibiting K-gene of *Wiener*.

The first mentioned two facts partly explain the disproportion referred to above, but if we disregard the explanation of *Wiener* as a highly hypothetical one since the gene K could not be demonstrated as yet there still remains a wide gap between the number of the M. h. n. cases observed and those that may be expected. This gap can easily be bridged if — as I have assumed — I. n. l. and I. n. gr. belong to the same pathological entity. If we try to bridge the gulf, we must be aware of the fact already mentioned, that there is a numerical disproportion between the percentage of I. n. l. found in the newborn and the number calculated on the basis of my isoagglutination-theory in its original form. The isoagglutination theory of the I. n. l. (ABO-icterus) was welcomed by the great scientist *Volhard* as the one — and I quote his words — «alone capable of furnishing a uniform explanation for the fetal and the postnatal bilirubinaemia». He had only one objection to my theory, namely the disproportion above mentioned.

Now new discoveries pointing beyond the four classic groups, i. e. the subdivision of A into A₁ and A₂, the isoagglutinins anti-A₁ and anti-0, the fact that immune agglutinins can be produced in an organism containing identical normal agglutinins, etc., made us recognise that I. n. l. can manifest itself in many other relations besides the classical agglutinophile ones. Approximative calculations on the basis of accessible data have shown that the number of the I. n. l. cases observed somewhat exceeds that of the ag-

glutinophile pregnancies. As mentioned above, the reverse is true for I. n. gr., the number of cases observed lagging far behind the expected number. In other words, the number of actually observed cases of jaundice is in one instance higher, in the other instance lower than the figure calculated. The difference amounts to approximately 10 % in both the positive and the negative direction in relation to the total number of pregnancies. — Two equal sums, entered one on the credit, the other on the debit side of an account, cancel each other and there is neither deficit nor surplus. The moment the pathogenetical unity of I. n. l. and I. n. gr. is recognized, it is not only permissible but actually necessary to consolidate the ledger account of the two. Evidently the 10 % surplus of I. n. l. cases has its origin in Rh-incompatibility and not in ABO-agglutination. Conversely the 10 % icterus which cannot be located among the cases of I. n. gr. may be found among the I. n. l. cases of ABO-type.

The next question to be dealt with is: why is it, that so many cases of Rh-icterus have been taken for I. n. l.? It should be emphasized that not every Rh-icterus is necessarily a grave one and in such cases the erroneous diagnosis of I. n. l. is, especially if the ominous Rh-relation of the parents has not been recognized, rather frequent. It is the jaundice of the first child, and if the father is heterozygous for Rh, possibly of the second and even the third child, which very often is not correctly diagnosed. Thus, the error may remain undiscovered and the children, entered on the page of I. n. l., never registered on the page reserved for Rh-cases. In these cases the physician contents himself with the diagnosis »physiologic jaundice» or »prolongated physiologic jaundice» or, occasionally, »grave anaemia of the infant age».

The ABO exceptions manifesting themselves as I. n. gr. constitute an everless difficult problem. As is generally known, intensity and extension of I. n. l. vary on a broad scale. Numerous cases have been observed in which a coincidence of circumstances (e. g. a high agglutinin-titre, the increased permeability of the placenta, etc.) produces such grave symptoms as to imitate an I. n. gr. (in other words: Rh-icterus) or some other manifestation of M. h. n. This will occur mainly with non-secretor fetuses whose

body-fluids are free of ABO-agglutinogens (*Levine*). The maternal antibodies will in these cases come into contact with fetal cells of vital importance just as readily as the anti-Rh does in an Rh positive fetus with practically no Rh-antigen in its body-fluids. Herein lies the explanation of the fact which cannot be explained with the Rh-factors, namely that in about 8 to 10 % of the M. h. n. cases the mother is Rh-positive, the child Rh-negative or Rh positive like the mother. What are the antigens against which the mother forms antibodies in such cases and how does agglutination and haemolysis in the fetus ensue? The answer is that while in some of these cases an erroneous or deficient factor determination which disregards one of the Rh-antigens, and in some a new antigen still awaiting discovery may be responsible for the phenomenon the majority of cases most likely comes from extremely grave cases of ABO-icterus.

Summary.

1) I. n. is due to isoagglutination (and isohaemolysis). As to its clinical course it may be an icterus neonatorum levis or gravis. As to the antigens and antibodies leading to isoagglutination the icterus is either an ABO-icterus or an Rh-icterus.

2) As a rule, the levis form is an ABO-icterus, the gravis form is an Rh-icterus, there being, however, exceptions.

3) The ABO-agglutinogens are soluble in water, the Rh-agglutinogens are not. Thus the former are present in the body-fluids (at least in secretors), the latter are not (or only in vestiges). The ABO-agglutinins of the mother react on the corresponding agglutinogens contained in the blood stream and on the body fluids of the fetus yet nothing prevents the anti-Rh agglutinins from gaining access to the erythrocytes and the parenchymatous organs. It is for this reason that Rh-icterus takes a more serious course and has an unfavorable prognosis.

4) The constellation promoting Rh-icterus (Rh-agglutinophilia) is considerably more frequent than icterus neonatorum gravis. ABO-agglutinophilia favoring ABO-icterus is, on the other hand,

considerably less frequent than the actually observed cases of icterus neonatorum levis. The not yet satisfactorily explained difference amounts to 10 % of all pregnancies in both cases, and is, no doubt, due to the fact that Rh-icterus often takes the clinical form of icterus neonatorum levis and is recorded with the levis cases, thus ostensibly increasing the number of the latter. The gap existing between the number of cases of ABO-agglutinophilia and of actually observed cases of icterus neonatorum levis is thereby filled.

5) In the rare cases in which an Rh-positive mother's child is suffering from icterus gravis (or other forms of morbus haemolyticus neonatorum), the role of as yet undiscovered agglutinogens and agglutinins has to be assumed. It is, however, probable that in the majority of instances they are nothing but extremely grave cases of ABO-icterus.

Discussion.

Charokopos, Sp. and Margaritis, J., «Kyriakou Children Hospital» at Athens, Greece: *Rh-factor in children diseases.*

During the last year, we typed the blood of 16 patients of «Kyriakou Children Hospital», and our private patients at Athens, parallel with the blood of the parents, by anti-Rh serum standard 85 % Lederle, following exactly the included directions for use. The results of our research are shown from the included table.

We note

1) that all patients were children of healthy parents, brothers and sisters where they exist.

2) By our information, we would not confirm in cases 9—16 the same clinical picture in members of the family, until the generation of grandparents.

Although the number of our cases is small, and therefore does not permit final conclusions, we would emphasize the need for Rh-factor determination principally in blackwater fever, favism, Cooley's anaemia and mental diseases of infancy. Such determinations, repeated in a large number of cases, may be hoped to solve the problem of etiology, pathogenesis, heredity, prophylaxis, and therapy of these diseases.

No.	Disease	Father		Mother		Sick child				
		O, A, B, AB	Rh	O, A, B, AB	Rh	No. of Birth	Sex	Age in years	O, A, B, AB	Rh
1	Microblast. anaemia	0	+	0	+	2	♂	7	0	+
2	" " " " " " " " " "	0	+	A	+	3	♂	8	A	+
3	" " " " " " " " " "	A	+	AB	+	1	♂	6	B	+
4	" " " " " " " " " "	B	+	B	+	12	♂	6	B	+
5	Kala-azar	0	+	B	+	1	♂	6	0	+
6	" " " " " " " " " "	A	—	A	—	1	♀	4	A	—
7	" " " " " " " " " "	0	+	AB	+	2	♀	6	B	+
8	" " " " " " " " " "	A	+	B	+	4	♂	4	A	+
9	Malaria (Black water fever)	A	+	AB	+	2	♂	4	AB	+
10	" " " " " " " " " "	B	+	AB	+	1	♂	5	A	+
11	" " " " " " " " " "	AB	+	A	+	2	♀	8	B	+
12	Favism	0	+	0	+	2		9	0	+
13	" " " " " " " " " "	A	+	B	+	1		8	AB	+
14	Cooley's anaemia.....	A	+	A	—	1		16 months	A	+
15	" " " " " " " " " "	A	+	B	—	2		2	B	+
16	Idiocy	B	+	B	—	1		12	0	+

Isoinmunización por el factor Rh.

Estudio sobre su duración en estado activo.

Por Dr. **Elias Halac.**

Prof. A. de Pediatría de la Fac. de Medicina y Director de la Escuela de Puericultura de Córdoba.

Dr. Humberto Linares Garzon.

Jefe de Investigaciones Factor Rh del Instituto de Maternidad y Jefe de Serología e Investigaciones del Instituto de Hemoterapia de Córdoba. Médico de la Escuela de Puericultura.

Dra. Mercedes Oliva Otero de Sacchetti.

Bioquímica Ayudante de la Sección Investigaciones Factor Rh del Instituto de Maternidad. Agregada a la Escuela de Puericultura de Córdoba.

(Abstract.)

1. La isoinmunización por el factor Rh en estado activo, o sea con presencia de anticuerpos anti-Rh en la sangre circulante, puede persistir durante toda la vida, como lo demuestra el

CASO 4 en que se comprobaron 33 años después del último embarazo.

2. La persistencia mayor o menor de los anticuerpos anti-Rh es una característica de cada individuo aunque en general, puede decirse que está en relación con el número, la frecuencia y la intensidad de los estímulos antigénicos recibidos. Los embarazos repetidos son más activos que las transfusiones únicas.

3. El transfusor debe hacer sistemáticamente, en toda mujer madre, un interrogatorio sobre la existencia de hijos con enfermedad hemolítica del recién nacido, cualquiera sea el tiempo transcurrido desde el último embarazo.

4. Es conveniente que los médicos sifilógrafos tomen un mayor conocimiento del rol desempeñado por la isoimmunización Rh en los casos de abortos repetidos y de polimortalidad fetal y neonatal, para evitar tratamientos específicos inútiles.

Congenital Malformations Induced in Rats by Maternal Nutritional Deficiency.

By **Josef Warkany, M. D.**

From the Children's Hospital Research Foundation, Department of Pediatrics, College of Medicine, University of Cincinnati, Ohio, U. S. A.

I should like to present to you three syndromes of congenital malformations induced in rats by dietary deficiencies of the mother. These studies were done in collaboration with Dr. Rose C. Nelson, Miss Elizabeth Schraffenberger, Mrs. Carolyn B. Roth and Dr. J. G. Wilson. The three experiments had the following points in common:

1. The mothers' diets were deficient in certain vitamins but the amount of food was not limited.

2. An attempt was made to create borderline deficiencies which would injure the developing fetus without killing it.

3. The males used in these experiments were fed an adequate stock diet.

Slight congenital anomalies of the skeleton can be induced in the young of rats bred on a diet deficient in vitamin D. Diet R

consists of the Steenbock and Black diet 2 965 (yellow corn meal 76, wheat gluten 18, calcium carbonate 3, sodium chloride 1) and 2 per cent dried pig liver. The supplement of liver facilitates breeding. The young born by mothers fed diet R appeared externally normal, but after clearing with the Schultze Dawson method (1), bowing of the radius, ulna, tibia and fibula was seen in 45 per cent of the young (2). When diet R was supplemented with vitamin D only normal young were obtained.

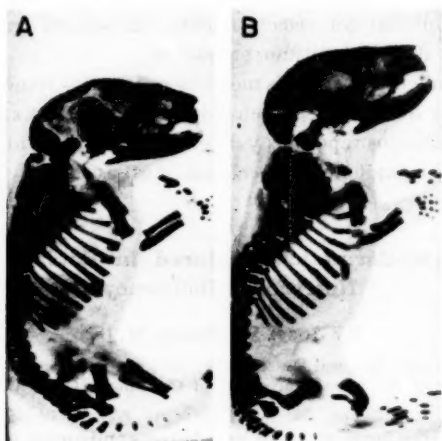


Fig. 1. A. Cleared specimen of normal newborn rat. B. Abnormal newborn rat, offspring of mother fed the rachitogenic diet R, showing curving of tibia and fibula and broadening and angulation of the ribs.

A slight change in the maternal diet R resulted in a completely different pattern of skeletal anomalies. When liver was omitted from diet R and vitamin D added, our diet I was obtained. This diet had the following percentage composition: yellow corn meal 76, wheat gluten 20, calcium carbonate 3, sodium chloride 1. A supplement of viosterol was added, each rat receiving 60 I. U. of vitamin D every tenth day. About one third of the young obtained from mothers reared and bred on diet I had congenital anomalies which in many cases altered the external appearance of the offspring. The mandible was short and the tongue pro-

truded. The extremities were frequently reduced in size and various degrees of syndactylism were observed. Cleft palate was present in about 44 per cent of the abnormal young. When the young were cleared, it was found that the anomalies conformed to a definite pattern of skeletal changes.

Shortening of the mandible, radius and ulna, shortening or absence of the tibia and fibula and fusion of the ribs could be visualized frequently. Some bones were often affected while others, such as those of the spine and skull were regularly spared (3).

It was soon found that liver added to diet I prevented these malformations. In a search for the preventive factor a mixture of five crystalline vitamins of the B-complex (riboflavin, thiamine, niacin, pyridoxine and pantothenic acid) was added to the maternal diet I and the abnormal pattern was prevented in the young. Supplements of thiamine, niacin, pyridoxine and pantothenic acid were ineffective. When, however, riboflavin was added to diet I, no abnormal young were observed. This seemed to indicate that a lack of riboflavin was responsible for the anomalies induced by diet I. But the crucial experiment remained to be done. On a highly purified diet in which the vitamin B-complex was represented by crystalline vitamins, the same skeletal anomalies were found in a part of the offspring when riboflavin was omitted. In the presence of riboflavin the pattern of diet I was not observed (4).

The third type of congenital anomalies was induced by maternal vitamin A deficiency. Hale (5) in 1933 reported the appearance of anophthalmos and microphthalmos in pigs and Anderson (6) observed diaphragmatic hernia in young rats whose mothers had been fed diets deficient in vitamin A.

In our experiments female rats were raised on a diet which contained enough carotene to make possible growth and maturation without permitting storage of vitamin A. During pregnancy the mothers were fed a purified diet which was entirely free of carotene and vitamin A (7). The young obtained from these females could be recognized externally by their edematous skin and in many instances by a lack of fusion of the eyelids, which is an anomaly in the newborn rat. More than 75 per cent of the

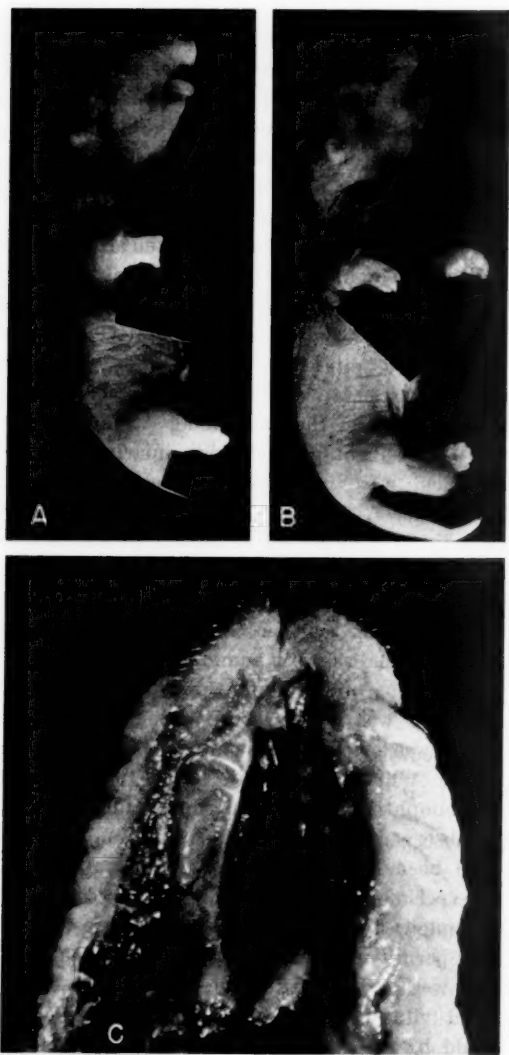


Fig. 2. Abnormal newborn rats, offspring of mother fed the riboflavin-deficient diet I. A—B. Shortening of the mandible, protrusion of the tongue and various degrees of syndactylism can be seen. C. Cleft palate.

Fig.

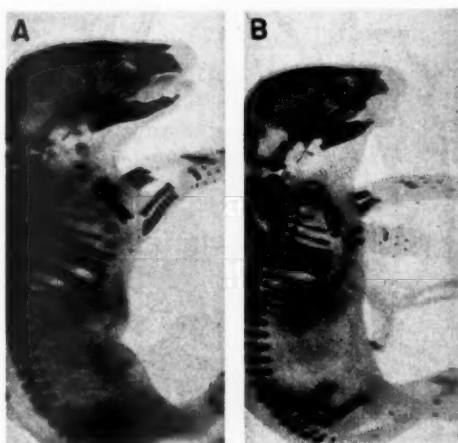


Fig. 3. Cleared specimens of abnormal newborn rats, offspring of mother fed diet I. Shortening of the mandible, radius and ulna, absence or shortening of the tibia and fibula and fusion of the ribs are seen.



Fig. 4. Abnormal newborn rat, offspring of mother bred on vitamin A-deficient diet. Edema and «open eyes» can be seen.

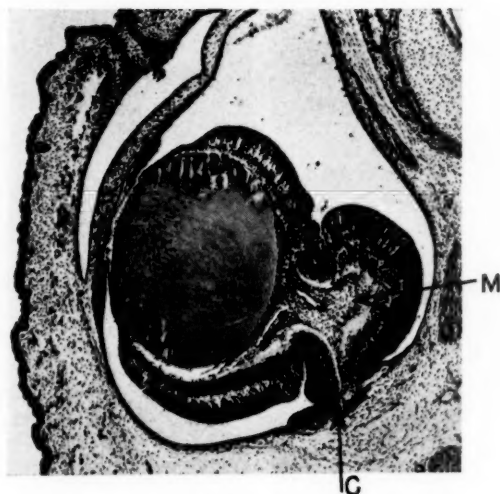


Fig. 5. Abnormal eye of newborn rat, offspring of vitamin A-deficient mother. The retrolenticular membrane (M), folding and coloboma (C) of the retina and rudimentary iris and ciliary body can be seen.

young had a retrolenticular membrane (Fig. 5, M) in place of the vitreous body. Coloboma of the retina (Fig. 5, C), rudimentary iris and ciliary body and other ocular anomalies were frequently present. In the chest a retardation of the development of the lungs, the pleura and of the heart was seen and frequently a lobe of the liver protruded through a defect of the diaphragm into the pleural space (diaphragmatic hernia). The kidneys seemed to be inactive since the renal pelvis and the ureters were not unfolded and horseshoe kidneys were occasionally observed. In addition there were changes of the urogenital ducts and it was frequently found that the ureter did not terminate in the bladder but in the urethra.

Thus, three syndromes of congenital anomalies have been induced in the young of mothers who were fed diets deficient in three vitamins: vitamin D, riboflavin and vitamin A. Time does not permit a detailed description of the technique of our experi-

ments, which I have presented to you as briefly as possible. Our aim was to induce congenital malformations in mammals and not to imitate dietary conditions in man. We do not think, therefore, that these experiments represent the answer to the intricate problem of human malformations; but they represent an experimental approach to this chapter of pediatrics which has hitherto been neglected.

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The Value of Administration of Synthetic Vitamin K before Labor.

By **Holger Dyggve, M. D.**

(From the University Lying-In Department, Copenhagen, Denmark.)

In Copenhagen I have studied the results of vitamin K prophylaxis in about 10 000 mothers as compared with about 10 000 controls.

The treatment was in most cases to give 1 cc of Synkavit intramuscularly at the onset of labor. The incidence of melaena or hematemesis or both in the treated group was 0.04 per cent and in the control group 0.20 per cent. In other words, the actual figures were only 4 cases in the treated group against 21 in the untreated.

I therefore believe that vitamin K should be given routinely to every mother not more than twelve and not less than four hours before delivery. If this is impossible, a similar dose should be given to the infant immediately after birth.

This same material is now being studied from the point of view of bleeding other than gastrointestinal, and will be published soon.

Section 2—Preventive Pediatrics.

Les maladies causées par le groupe *Salmonella* en rapport avec les diarrhées saisonnières chez les enfants.

By **Henryk Brokman**, Gdańsk, Poland.

Nos observations aussi bien cliniques, que bacteriologiques anciennes et actuelles, ont confirmé un fait connu, que les bactéries *Salmonella* peuvent provoquer au point de vue clinique trois types de maladie.

1. L'aspect clinique de la fièvre typhoïde.
2. Intoxication par les aliments (surtout par la viande).
3. Type septique avec localisation dans les divers organes.

Nos observations au courant de la dernière année sur la côte polonaise de la Baltique appartiennent au 3^{me} groupe. Dans la clinique pédiatrique à Gdańsk nous avons constaté une méningite purulente chez 4 nourrissons, causée par *Salmonella enteritidis* Gaertneri, sans symptômes dans d'autres organes. Chez 2 nourrissons, chez lesquels on a pu démontrer la présence des mêmes micro-organismes dans le sang ou dans la moelle osseuse, l'aspect clinique présentait une bronchopneumonie. Dans un cas, après 10 jours de fièvre une pleurésie purulente s'est déclarée, terminée par la mort. Chez un nourrisson, chez lequel on a trouvé *Salmonella paratyphi B*, les premiers jours la maladie donnait l'aspect d'une encéphalite grave.

Ces observations ne diffèrent pas des observations d'autres auteurs et à ce qu'il paraît il n'y a pas de doute, que les *Salmonellas* constituent ici un facteur étiologique primaire.

Par contre à notre avis les microorganismes sont des facteurs étiologiques secondaires dans les diarrhées saisonnières chez les nourrissons et les petits enfants. Nos recherches conduites depuis

1927 ont démontré qu'aussi bien dans les formes légères, que dans les formes graves, évoluant sous la forme «toxicose» (toxique) on peut obtenir une culture des bactéries du groupe *Salmonella* du sang et des selles. Le pourcentage des résultats bactériologiques positives atteint dans certaines années 50 %. Il est à remarquer qu'en même temps on a obtenu des cultures des bactéries de certains types de paratyphoïde chez les enfants avec le même aspect clinique. De même, une endémie, qui a eu lieu dans une crèche d'usine, par conséquent dans un milieu fermé, a donné une flore bactérienne variée. La fréquente présence des symptômes d'otite, d'antrite et du rocher dans la majorité des cas au début de la maladie montre des rapports épidémiologiques dans tout le groupe des diarrhées saisonnières. Du pus de l'oreille on obtient parfois des cultures du groupe *Salmonella*. A notre avis l'otite au cours de l'évolution de la diarrhée saisonnière si souvent discuté n'est ni la cause des symptômes cliniques particulièrement intestinaux, ni la complication, mais il faut la considérer comme un des symptômes au cours de cette maladie. Ces observations nous ont conduits à la déduction logique suivante: dans les diarrhées saisonnières c'est probablement le virus, qui est le facteur provoquant la maladie, tandis que le groupe *Salmonella* ou la paratyphoïde jouent seulement un rôle secondaire, ou bien nous avons à faire dans cette maladie avec une unité morbide à étiologie complexe. Le point de vue, que les diarrhées saisonnières sont provoquées par le virus, énoncé par nous un peu hardiment déjà avant la guerre, trouve maintenant sa confirmation indirecte dans les travaux des auteurs américains, qui ont établi l'étiologie du virus dans le syndrome «stomatitis et les diarrhées» (Buddingh and Dodd), ainsi, que dans les diarrhées épidémiques des nouveau-nés (Light and Hodes). Auparavant pour motiver notre point de vue nous faisons l'analogie entre le rôle du groupe *Salmonella* dans les diarrhées saisonnières et le bacille *hemophilus* de l'influenza. Aujourd'hui cette analogie apparaît encore plus frappante en considérant l'ictère catarrhale, maladie provoquée par le virus, où les germes *Salmonella* sont souvent des facteurs secondaires.

Nous voudrions proposer l'organisation des recherches comparatives faites dans différents pays selon un plan préparé à

l'avance et à l'aide des méthodes standardisées. De cette façon nous aurions atteint peut-être plus vite la solution du problème d'étiologie d'une maladie, qui cause tant de victimes surtout dans les pays au bas standard de vie et en même temps construire des bases à une action prophylactique, car les méthodes générales d'hygiène employées jusqu'à présent ne paraissent pas suffisantes.

Breast Feeding in China.

By **Yung-En Kao, M. D.**

Department of Pediatrics, Moukden Medical College and Hospital, Moukden;
Division of Pediatrics, National Kweiyand Medical College and Hospital,
Kwei-chow.

Breast feeding supplies the natural and ideal food for infants. It plays a very important part in the reduction of morbidity and mortality of the Chinese infants.

In ancient times, there was a very good Chinese custom of sending gifts to the mother right after her confinement. This custom is still very popular even today. On the third day relatives and friends bring presents to congratulate her on the newly born. These presents naturally make the mother happy. Most of them are articles of food which nourish the mother and indirectly the baby. The gifts vary and range from 2 to 10 in number. The commonest present consists of 4 kinds out of the following:—eggs, chickens, noodles, pork, sugar, pig's knuckles, sesame etc. As to the quantity of the present, the number of eggs amounts to from ten to a hundred, sugar, wheat flour or sesame weighing from 4 to 10 catties, and one pig's knuckle or two. Generally the mother who has been delivered of her first baby receives more present than subsequent ones. A mother would receive from 5 to 40 times such presents. Some mothers may even receive as many as 100 or more. These gifts play a very important role in the production and maintenance of lactation. In most cases the presents are enough for nutritional purpose for the first one or two months. In this way Chinese mothers have milk sufficient for the need of infant for the first two to three months. For the

well to do, additional gifts for the newborn infant consist of clothing, cradle, cup, shoes, socks, quilts, pillows and others. Presents also come in the form of bracelets, neck-lace and other gold or silver ornaments.

After the birth of the baby, in North China, the mother lives almost exclusively on millet porridge, hard boiled eggs and chicken soups, which are considered most nourishing.

From the beginning of 1932 to August 1935, 6 920 children were brought to the Pediatrics O P D of Moukden Medical college and Hospital for treatment and 503 for advice. From the beginning of 1939 to the end of 1945, 17 342 children attended Pediatrics O P D of National Kwei-yang Medical College and Hospital for treatment, 673 for physical examinations, 554 for advice and 665 for vaccination. These children totaled 26 647 as outpatients. Based on the analysis of these 26 674 cases, it is found that 95 % of the Chinese infants are fed on mother's milk. The mother considers it her duty to feed her own baby. As a rule every Chinese mother is more than willing to feed her own infant. However a few mothers who are healthy and well educated are averse to breast feeding. Their babies will have to depend on wet nurses or artificial feeding.

According to Tso's series (1) of analysis of milk obtained from 87 Chinese mothers' milk, the composition is «protein 1.36, fats 3.72, carbohydrates 7.14». It does not differ to any appreciable extent from mother's milk in the west.

In our series, 10 % of the cases, show that breast feeding is given every 4 hours, 20 % every 3 hours and 70 % irregularly. For delicate, undernourished or premature infants feedings on 3 hours schedule are desirable. Irregular feeding may cause indigestion, restlessness, and colicky pain. Feeding at 4 hour intervals is undoubtedly most beneficial. In fact in large towns in China, there is already a tendency to feed infants on this schedule. Night feeding is also commonly practised. Sometimes as high as 85 % in our series. This high incidence is to be accounted for by the fact that the mother and her infants usually occupy one bed.

It is universally recognized that the weaning of an infant is a very important problem. In Europe and America the best

time for weaning is while the baby is between 8 and 9 months old (2, 3, 4) although some authorities (5, 6, 7) maintain that the infant should be breast fed until it is 10 months or one year of age. In China, we have obtained the following data on weaning after analysing a series of 26 447 cases:

TABLE I. Time of Weaning.

Age of the infants	Number of infants weaned
6 months	461
7 months	519
8 months	1 545
9 months	2 755
10 months	3 521
11 months	3 509
1 year	12 216
1 $\frac{1}{2}$ year	1 100
2 years	623
3 years	205
4 years	112
5 years	72
6 years	21

It is clear from the above table that most Chinese infants are weaned at the age of one. A small number of children continue on breast milk to the sixth year of age, but in these cases, breast feeding is supplemented by other foods.

The problem of wet nursing in China is of considerable interest. In the city of Moukden, it was found that about 5 % of the infants were fed by wet nurses, while in Kwei-yang, only 1 %. The differences may be explained by the fact that in Moukden, the people were well off and could afford a wet nurse even for the middle class, whereas in Kwei-yang the financial condition of the populace in general was bad, especially during the war.

The reasons for employing wet nurses are:— (1) wealthy parent may not like to be bothered with the nursing her own infants, (2) mothers are forced to give up nursing their own babies because of such serious illness as sepsis, typhoid fever, bacillary dysentery, uterine haemorrhages: and (3) mother die sometimes during the period of lactation.

Generally speaking, in China, nobody likes to be employed as a wet nurse. But under certain circumstances, such as poverty

and other troubles often force women during their lactation period to seek employment as wet nurse.

The great majority of wet nurses in China are well-behaved and good tempered. Their age range from twenty five to thirty five usually recommended by relatives or friends of the babies' parents, and as a rule, they are considered a member of the household. Two-thirds of them in our series fed male infants, while one-third fed the female. Employments begin after the birth of her own baby one month, two months or even a year. Three quarters of the infants in our series were fed by one wet nurse without change. Only one-quarter have their wet nurses changed from two to as many as twelve times. Repeated changes of wet nurses may resulted in the infants being contaminated with syphilis, tuberculosis, eye and skin diseases. It is a common practice now for the wet nurses, before being employed to undergo complete and thorough physical examination.

Summary.

From the beginning of 1932 to August 1935, 6 920 children were brought to the Pediatrics O P D of Moukden Medical College and Hospital for treatment and 503 for advice. From the beginning of 1939 to the end of 1945, 17 342 children attended the Pediatrics O P D of National Kwei-yang Medical College and Hospital for treatment, 673 for physical examination, 554 for advice, and 665 for vaccination. These children totaled 26 647 as out-patients.

The findings from breast feeding are listed below:

1. The custom of sending gifts to nursing mothers right after confinement is discussed.
2. 95 percent of Chinese babies are breast fed.
3. The composition of Chinese women's milk as determined by Tso has been mentioned.
4. In our series, 10 percent of the cases received breast feeding every 4 hours, 20 percent every 3 hours, 70 percent irregularly.
5. Weaning usually takes place after one year of age in most instances.

6. Wet nurses supply 5 percent of breast feeding in Moukden, only one percent in Kwei-yang. The probable reason being high cost of living.

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Preventive Paediatrics in Sweden.

By **A. Lichtenstein**, Stockholm, Sweden.

In Sweden preventive child care is regulated by a number of laws. The oldest Swedish law concerning the care of children dates from the 12th century. A State orphanage was founded in 1633. In the middle of the 18th century, Rosén von Rosenstein published his articles on the care and treatment of children in the »Almanachs» and these articles were collected in his famous book »Information about Diseases of Children and their Cure» (1764). From that time we note a growing interest for public child care in Sweden. During the 18th and 19th centuries, a succession of Acts regarding child welfare were passed, for instance the »Act Regulating the Rights of Illegitimate Children» of 1788. Our first day-nursery dates from 1836.

During the 20th century there was a rapid development. A revision of the Law regarding Illegitimate Children in 1917 instituted a child welfare guardian for every illegitimate child. The *Child Welfare Act* of 1924 imposed on every community the duty of organizing a child welfare committee. Public care, protective upbringing and the care of foster-children are regulated by several

laws, and the care of children both at home and in institutions, is improving year by year.

Maternity and Child Welfare Centres.

Our most important weapon in combating morbidity and mortality in children is our *maternity and child health service*, which is state organized and based on a law of 1937. In *prenatal clinics* every prospective mother can be periodically examined free of charge. About 60 % of all prospective mothers in Sweden, — and in some towns up to 80 % — were under such control in 1945. We have regulations for maternity aid and are endeavouring to enlighten mothers by means of classes for prospective mothers, as well as by instructive booklets and broadcasts.

The child welfare centres, which today cover the whole country, are organized as follows: Centres of type I, generally in the larger towns, are under the charge of a trained paediatrician aided by a fulltime nurse. Centres of type II are intended for smaller towns and closely populated areas without access to specialist. Type III, the maternal and child welfare stations, are spread all over the country. At these stations, the care of the mothers and children is entrusted to the provincial Medical Officers of Health, with the aid of the district nurses and district midwives. The total sum of maternity and child welfare centres in 1945 was 1 303, the number of surgeries held 51 599.

Attendance at the welfare centres is entirely voluntary. Of 134 000 children born in 1945, 111 000 (or 85 %) were periodically examined at these centres. In certain towns the percentage under control is even higher.

The centres are supervised by the Royal Medical Board and are state subsidized. The consultations are entirely free of charge. In the child welfare centres, only health care is given, whereas at the maternity centres, diseases of pregnancy are also treated.

The control of the children is carried out in the surgeries by the physician and in the homes by the nurse. One of the most important tasks of our centres is, in my opinion, propaganda for breast-feeding and overcoming the difficulties in this connection. In the years 1938—1945, 70—80 % of the infants under control

were entirely breast-fed for at least 2 months, and 42—43 % for 6 months. If breast-feeding is not feasible, the centre gives advice as to suitable artificial food.

Prophylactic measures are taken against rickets and anaemia. Where necessary prophylactic medicines, cod-liver oil, iron and calcium, as well as fruit and vegetables can be requisitioned free, and are paid for by the State.

In the child welfare centre, compulsory vaccination against smallpox is performed. Other vaccinations in Sweden are voluntary. Vaccination against diphtheria and tuberculosis is, however, performed on a large scale. Vaccination against whooping-cough and influenza, as well as serum prophylaxis against tetanus and measles, lately with γ -globulin as well, is carried out on a minor scale.

During the first years, infants only were admitted to the centres. We are now endeavouring to bring all children of pre-school age under control. In some towns, for instance in Stockholm and Gothenburg, all children up to school age already have this advantage. In other parts of the country, children up to 2 or 3 years of age are under control. In 1945 56 % of all children between 1 and 2 years were periodically examined, 24 % between 2 and 3 years, but only 4 % of the children between 3 and 6 years of age. This situation is now improving, but the lack of a sufficient number of trained paediatricians and insufficient paediatric training for state-appointed public Officers of Health place certain obstacles in the way of further development.

Health Care of School-Children.

The school health service has developed since the end of last century, but has for a long time left much to be desired. After the appointment in 1943, of a Head School Physician, attached to the Central Board of Education, the school health service has been organized on uniform principles. Our three largest cities have their own Chief School Physicians paid by the municipality. Every secondary school has a part-time school physician. Medical Officers of Health are attached as school physicians to the elementary schools. Private schools also have their own physicians. The com-

prehensiveness of our school health service is illustrated by the fact that about 1 000 physicians of a total number of about 4 500 physicians in Sweden participate in the school health service. Our aim is to place every child at school under the supervision of a competent school doctor. Training in paediatrics is, as a rule, a deciding factor in the appointment of a school physician.

School nurses are attached to secondary as well as to elementary schools as assistants to the school physicians. They also visit the pupils in their homes when necessary.

The school health service is a preventive service. Treatment of disease is not a task for the school physician. It must, however be borne in mind that it is often difficult, in practice, to draw the line between health care and the treatment of disease.

In 1946, the Swedish Parliament passed an Act entitling all school children to one daily meal at school free of charge.

On starting school, a *personal health card* is issued to each pupil and this accompanies him throughout his school years. When he leaves, his card is sent to the State Institute for Human Genetics and Race Biology, where it is accessible for research work.

Mental Care.

The preventive mental care of children is at present organized by the State. Our aim is to have as a leader of this activity a child psychiatrist in each county, assisted by a psychologist and social workers. This scheme has however hitherto only been carried out on a minor scale.

In a number of towns we have *child guidance clinics*, partly attached to children's hospitals, where children with difficulties of adaptation are accepted in large numbers for more thorough investigation.

Dental Care.

In 1938, an Act was passed concerning public dental care. This organization will be extended to make it possible for all children from 4 to 15 years to be treated. The present charge is very low, and is fixed at 5 Swedish crowns (about 1.25 dollars) a year per child. In many counties, the entire charge for dental care is borne by the authorities.

Our preventive measures are completed by a large number of institutions such as summer camps, children's homes and day-nurseries. Owing to the short time at my disposal, no more than a mention of these institutions is possible. I must also state that we can note a tendency in Sweden during the last years against collective child care, especially on account of the frequency of cross-infection. This question is for the time being a subject of thorough investigation in our day-nurseries.

The most important factors which bring about a decrease in a country's mortality are improved conditions in general hygiene, improved standards of living and increasing general enlightenment. We also find that infant mortality in Sweden has decreased from over 20 % in the beginning of the 18th century to approximately 3 % in 1945. The question remains: is still the gradual decrease in infant mortality perhaps only due to the previously mentioned causes? ÅKERRÉN in Sweden has, however, made an interesting observation in this respect. When studying infant mortality during the period from 1911 to 1943 he found that the decrease for each 5-year period — earlier about 6 ‰ — in the nineteen-twenties without obvious reasons fell to about 2 ‰. In the 30's, public child welfare developed rapidly. During the following 5-year periods, the decrease in infant mortality rose to 7.5 and 8.2 ‰. The latest figure is 10.6 ‰.

My paper today shows that our preventive work in paediatrics in Sweden is state organized. In my opinion, a state organization and a substantial state subsidy and control are necessary, if the health care in a country is to function effectively and satisfactorily. The fears expressed by some doctors, that a state activity in this field would hamper or prevent the practising doctor's exercise of his profession, have proved themselves to be unjustified. On the contrary, the work, for instance of our child welfare centres, has increased the interest of the public in child welfare and private paediatricians are busier than ever before. If we endeavour to keep as strict a borderline as possible between prophylactic and curative medical care, then I do not believe that the former will in any way hamper the latter. This, however, presupposes that the state

medical activities are not so organized as to make private medical practice impossible. There is a risk in medical bureaucracy, and we must guard and foster that personal contact between the patient and the doctor, which is a necessary condition for all satisfactory medical activity. A socialization would, for the medical profession, mean a lowering of standards, which is in direct opposition to the interests of the country. The duty of the state is, however, to organize medical care in such a manner, that every person, irrespective of his income, can obtain the best medical care.

In my opinion, the Swedish system shows very clearly that this can be done without undermining private medical practice.

Pediatric Surgery in Mexico.

By Dr. **Jesús Lozoya S.**

Head Resident of the Surgical Department of the «Hospital del Niño» in Mexico City.

Pediatric Surgery, at the present moment, is in a state similar to the one in which Medical Pediatrics was 50 years ago. At that time neither the Medical Doctors nor the public at large realized the need of physicians specialized in the care of babies and children; the family doctor took care of all the members in the family from the grandparents to the grandchildren. Now we see children being cared for by well trained pediatricians in any city or town of importance in any part of the civilized world. That situation which prevailed regarding Medical Pediatrics some years ago is now actual, regarding surgical problems in children. These problems are being solved by the surgeon non specialized who can never obtain enough experience in dealing with the special problems that children present, with the inevitable result of the very high mortality that statistics still show in surgical cases among children.

It is not easy for the general surgeon to really control all the varied specific problems of Pediatric Surgery and to realize how very important these problems are. At most, the general surgeon or the specialist in any other branch of surgery develops some

interest for one of the many problems of Pediatric Surgery (for instance congenital heart malformations) and they may realize marvellous advances in this line; but — they do not constitute a general surgical service, only and — exclusively for children, where these shall be studied and — cared with the combination that is required of a well grounded pediatric and surgical knowledge. Most all the surgeons handle these cases as if they were «little adults», without a correct appreciation of the special requirement of hydroionic balance, of diatetics, education and all the common diseases of children, that can create all sorts of complications.

Not until Pediatric Surgery could develop by itself the mortality rate in surgical problems among children — very remarkably in the first days after birth — lowered from terrifying — numbers to rates that fill us with hope. But this state could be reached only when some few surgeons scattered here and there in the world, devoted all their efforts for 20 or 30 years to the study and treatment of these problems, confining themselves to children *exclusively*. When men like Ombredanne in Paris and Ladd in Boston gave their whole life to the practice of surgery exclusively in children, creating services and schools that go beyond their own time and place, surgeons and physicians in — general began paying attention to Pediatric Surgery. Unfortunately there have been few men like these, and that is why — Pediatric Surgery is yet in the conditions we mentioned at the beginning of these words. These masters in surgery left us — their schools but we fear that in time these schools loose their point of «Schools of Pediatric-Surgery» and that the new men — formed in them may dilute themselves in the current of general surgery for adults and children, arriving even to be more of a handicap, than a help, for the extension of pediatric surgery; this phenomenon occurring because the great extraordinary surgeons who opened this new road, were not specialized pediatricians before entering pediatric surgery.

We are convinced that pediatric surgery has its own problems which were fatal until lately (like: atresia of the — esophagus, atresia of the intestines, malformations of the — peritoneum, or

of the bile passages, congenital malformations of the heart and so on). These were never properly handled — before, unless the surgeon had a special inclination for surgery in children and could count with a well organized pediatric service, where pediatricians often called those surgeons to their aid and urged them, even pushed them, to take hold of the problem and solve it. Besides the same general problems of surgery, be it in children or in adults like the pre and post operative care, have their own character in children, — (for instance, the hypersensibility of children to hemorrhage, to dehydration, to the changes in temperature; the requirement not only of keeping up the organism but of leaving margin for the development of the body in full period of growth if those that handle them are lacking the necessary pediatric grounding, we have very sad statistics.

Nobody doubts now, that the surgeon, besides being a perfect operator and having remarkable skill, has to be a good — clinician, with a solid preparation and full knowledge of medicine in general; following the same line of thought we are — convinced too that the good pediatric surgeon, must be first a good pediatrician.

The «Hospital del Niño» of Mexico City, felt this need for pediatric surgery. In a general children's hospital like this, where children ought to find adequate treatment for all the ailments that can come to men from birth to the adolescent period inclusively, there must be a service of Pediatric Surgery, where surgeons operate only on children, but where these surgeons receive also sufficient pediatric information so as to be considered as pediatricians in any well qualified institution in the world.

We have not been able to secure pediatricians specialized in pediatric surgery for the different branches of surgery like eyes, orthopedics, neurosurgery etc., but we have tried to make the specialists of these different branches have a constant, — daily, intensive, practice with children. In general surgery we have been able to make so as to have all the members of the staff go first through a complete internship in pediatrics; and of course, before coming to the internship they have had already some experience in general surgery. This way we are giving a complete formation to our pediatric surgeons, as clinicians and as surgeons,

but confining themselves only to children. Among this group we try latter on, to lead some of them towards the different branches in surgery; so we hope in 10 years from now, all the branches of the Surgical Service of the Hospital will be in the hands of pediatric surgeons, specialized (as a second specialization) in each line of surgery.

The intern in Pediatrics rotates and covers 2 years; then they have 2 years as subresidents and 4 as minor surgical residents; then they can go as visiting surgeons in some of the specialized lines (like orthopedics, endoscopy, otorhinolaryngology, etc.) or as Resident Surgeon, to obtain the grade «Master in Pediatric Surgery».

The Surgical Sub-Residents rotate also in their 2 years-period, having 8 months in each of the three following groups:

- 1.— General surgery, plastic, thoracic, urological and — neurosurgery.
- 2.— Orthopedics and dental surgery (maxillofacial).
- 3.— Otorhinolaryngology, endoscopy, eyes, surgery in — cadavers and animals.

In as far as the economic problem for the pediatric surgeon, we believe that we are giving them a good preparation to solve it in the field of children only, without having to invade the field of adults. It can be argued that he can not — have a full control of such a vast field; but we think that, at least, he can be a *good general surgeon for children*, and considering the general situation of medicine in the present days, we feel sure that children will be greatly benefited.

Until now the «Hospital del Niño» in Mexico City is — unique in the world as a general hospital only for children and having a complete surgical service, plastic, thorax, — urology, endoscopy, dental, orthopedics, eyes, otorhinolaryngology and neurosurgery, all organized according to above — quoted plan. Its staff is formed by a Head Resident and 42 Surgeons; it has 250 beds (nearly half of the full capacity of the institution, which is of 600 beds), 5 operating rooms and an average of 20 operations daily. It serves as a concentration hospital for all the Mexican Republic; therefore the number of cases is very large, showing all

sorts of varieties and of great interest. We feel convinced that in this way, in 10 years, — pediatric surgery will be recognized as a special branch of — medicine; the problems in children will be dealt in better form and the field of pediatrics will be enlarged by the contribution from this branch, approaching its ideal of helping children and adolescent boys and girls to solve their problems of health.

Summary.

Pediatric Surgery is now going through the same conditions that affected Pediatrics in General 50 years ago.

Today General surgeons, in most hospitals in the world, — must operate without counting with services properly adapted to this technique; yet pediatric surgery has problems of its own and even those that affect both the adult and the child — have to be handled in a special way since children have their own peculiarities.

The general surgeon can never arrive to have a complete control of the pre and post operatory conditions and even of the intervention itself because they lack a good solid foundation as pediatricians. They think of the child as if it were a «little adult» as a consequence mortality in cases of surgery among children is still very high.

Professors like Ombredanne in Paris and Ladd in Boston — have opened the way to pediatric-surgery by devoting their — whole lives for 20 or 30 years to operate exclusively in children; but there are not many like them, therefore pediatric-surgery is not yet generally accepted and there is even the — danger that it shall not be recognized as an specialization — inside pediatrics, because the principal exponents of this new branch have not received a foundation in pediatrics.

Every body agrees now in asking the surgeon to be also a well rounded clinician; with similar convictions we are asking the pediatric-surgeon to be first a good pediatrician.

The «Hospital del Niño» in Mexico City which is a general hospital for children, representing this new attitude, established a service for pediatric-surgery from the first day it was opened to

the public. The service counts with 250 beds (600 is the total capacity of the Institution) these are divided among: general surgery, plastic, thoracic, urology, neuro-surgery; — maxillo-facial, orthopedics, endoscopy, eyes, and practice is done on cadavers and animals.

The interns must have first 2 years internship in pediatrics rotating through all its services; (it is a previous requisite to have had some practice in surgery before entering) then, they have 2 years as subresidents rotating exclusively in the pediatric surgery department, then 4 years as minor resident in the same service and finally they can be resident in order to obtain the degree of «Master in Pediatric-Surgery».

The staff of the service counts with one head resident surgeon and 42 surgeons. We have an average of 20 operations daily; there is a large variety of cases and of great interest.

We have not been able to secure pediatric surgeons for the different branches as orthopedics neurosurgery etc.; but we hope in ten years from now all those places will be covered by surgeons having had the training we described above.

We feel sure that children will be greatly benefited when treated by general pediatric-surgeons instead of being operated upon by specialist who deal mainly with adults. The field of pediatrics will be enlarged, with this new line and it can — enhance all the care of the child and the adolescent.

Protection de la santé des enfants en URSS.

Par le Professeur **A. F. Tour.**

Membre-correspondant de l'Académie des Sciences Médicales de l'URSS.

En URSS, les questions se rapportant à la santé des enfants et à leur éducation sont l'objet d'une attention toute spéciale. C'est l'Etat qui prend soin de la jeune génération, et cette sollicitude, — ainsi, du reste, que tout le système de la Santé Publique, — constitue une partie intégrale du régime soviétique.

Ce qui caractérise surtout l'organisation de la Santé Publique

au pays des Soviets, c'est la prévention des maladies par la suppression des causes qui les provoquent. Cette intention prophylactique apparaît nettement dans l'ensemble des mesures élaborées pour l'assistance de l'enfance, mesures intimement et logiquement liées à celles prises pour l'assistance de la maternité. Le but essentiel qui en détermine la tendance et les fins, a été exposé en des termes pleins d'humanité et de simplicité dans le décret promulgué à ce sujet au mois de décembre de 1917: «Les mesures à prendre pour l'assistance de la maternité et de l'enfance,» y lit-on, «ont pour but de conserver la mère à l'enfant et l'enfant à la mère»...

Notre système d'assistance de la maternité et de l'enfance embrasse toutes les questions se rapportant à l'organisation du travail des femmes à l'assistance pendant l'enfantement, à l'alimentation, aux soins et à l'éducation à donner aux jeunes enfants, aux mesures nécessaires pour améliorer leur santé, à la prophylaxie des maladies infantiles et aux efforts tendant à réduire la mortalité des enfants.

La protection de la femme en général et de la femme enceinte en particulier constitue l'élément principal dans la *protection de l'enfant pendant la période prénatale*; celle exercée envers les mères et mères-nourrices en particulier, est l'un des faits principaux dans la *protection des nourrissons*. Dans ce bref aperçu il m'est impossible de m'arrêter au long sur toutes les mesures ayant trait à la protection de la femme et je me bornerai à n'en citer que quelques-unes se rapportant immédiatement à la protection de l'enfant.

Dispensaires pour femmes («consultations pour femmes»). Ceux-ci sont la première étape dans l'assistance de l'enfance. Immédiatement après constatation de la gravidité, la femme enceinte devient l'objet d'une observation régulière et ininterrompue de la part des médecins du dispensaire. Ceux-ci suivent attentivement l'évolution de la gravidité et l'influence qu'elle pourra avoir sur l'état général, font pratiquer tous les examens et analyses de laboratoire nécessaires et traitent, s'il y a lieu, les maladies gynécologiques. Au cas où des affections des autres organes se manifesteraient, le médecin du dispensaire envoie la malade dans une polyclinique où elle est soignée par des spécialistes. L'histoire des gravidités et des enfantements antérieurs est toujours soigneuse-

ment étudiée afin de prévenir les complications qui les avaient accompagnées.

Les données des examens cliniques et de laboratoire sont notés dans une fiche qui accompagne la parturiente lorsque celle-ci entre à la maternité.

C'est aux dispensaires qu'incombe un travail culturel important — celui d'inculquer aux mères futures les connaissances nécessaires pour les préparer à la maternité et aux soins qu'exigent les nouveau-nés, et de leur enseigner les règles à suivre pour l'allaitement et l'alimentation de leurs enfants.

Les dispensaires et les maternités, ou bien les services d'obstétrique des hôpitaux locaux s'informent mutuellement de tout ce qui concerne leurs malades.

Les *maternités* constituent le deuxième chaînon du système de l'assistance de la maternité et de l'enfance.

Depuis l'avènement au pouvoir du gouvernement soviétique le nombre des lits pour parturientes s'est fortement accru. Dans les grandes villes et les cités ouvrières 100 p. 100 des parturientes sont hospitalisées.

Quant aux villages ceux-ci sont desservis par un vaste réseau de services de maternité faisant partie des hôpitaux de district, de maternités de *kolkhoz*, d'ambulances, ce qui assure à la population campagnarde les soins de médecins et de sage-femmes diplômées.

Au cas où une observation suivie ferait prévoir quelque anormalité pendant la parturition, ou bien s'il y a eu antérieurement des avortions, des accouchements précoces, des symptômes de toxicopathie, etc., les malades entrent quelques semaines avant l'enfantement, aux services de «prématernité» près les hôpitaux pour femmes ou les maternités, où elles sont soumises à une observation constante par des médecins-accoucheurs spécialistes.

En URSS tous les efforts sont faits pour la prévention des maladies et le décroissement de la mortalité des nouveau-nés. Réduire celle-ci au minimum, obtenir une survie maximum des nouveau-nés, même lorsqu'il s'agit d'enfants faibles ou venus avant terme, réduire le nombre des traumatismes pendant l'enfantement, réaliser au mieux la prophylaxie des pneumonies, des

septicémies et autres affections des nouveau-nés — tel est le but que s'est proposé la médecine soviétique. Beaucoup de nos maternités ont déjà obtenu des résultats excellents sous ce rapport. Dans notre service des nouveau-nés à la clinique d'obstétrique de l'Institut des médecins-pédiatres à Leningrad la mortalité globale des nouveau-nés ne dépasse guère 2 p. 100 et le nombre des enfants venus avant terme ne constitue que 0,6 p. 100. Dans notre clinique spéciale pour les enfants venus avant terme, où le poids de la grande majorité des enfants admis est au-dessous de 2 kg. à la naissance, la mortalité varie entre 12 et 14 p. 100. Or, nous considérons que ce chiffre de la mortalité des enfants venus à terme et avant terme peut être encore réduit.

Dans les maternités les enfants sont séparés de leurs mères; on ne les apporte à celle-ci que pour l'allaitement. Les enfants nés faible ou avant terme, les enfants malades ou nés de mères malades sont placés dans des salles spéciales, desservies par un personnel choisi et soignés par des pédiatres et des infirmières diplômées; les infirmières non-diplômées (les bonnes) ne sont point admises à leur chevet. Tous les traumatismes à l'enfantement, tous les cas de maladies et de mort néo-natales sont soigneusement étudiés par les médecins-pédiatres, les médecins-accoucheurs et les pathologistes à l'autopsie. Les nouveau-nés restent à la maternité jusqu'au 9^e ou 10^e jour de leur vie; en cas de maladie, le séjour est prolongé d'office.

A Leningrad, à Moscou et dans quelques autres villes, les enfants venus avant terme et exigeant une alimentation et des soins particuliers, sont placés avec leur mères quand ce sont celles-ci qui les allaitent, dès qu'ils quittent la maternité, dans des cliniques spéciales pour enfants nés avant terme, où ils séjournent pendant 2, 3, 4 mois, ou même davantage, jusqu'à ce que leur état ne nécessite plus d'alimentation spéciale et de soins particuliers.

Pendant leur séjour à la maternité les nouveau-nés sont vaccinés contre la tuberculose (d'après Calmette).

Un échange constant d'informations existe entre les services pour nouveau-nés des maternités et les dispensaires pour nouveau-nés. Chaque fois qu'un nouveau-né quitte la maternité, celle-ci en informe le *dispensaire* de l'arrondissement où est domiciliée la

mère, et le médecin ou l'infirmière-visiteuse viennent immédiatement le visiter.

Les dispensaires ou «consultations pour nouveau-nés» constituent l'élément le plus important du système de la protection de la santé des nouveau-nés; ils sont chargés de veiller à la santé des jeunes enfants jusqu'à 3 ans. L'énorme majorité des enfants de cet âge sont régulièrement observés par les médecins de ces dispensaires, et aucun effort n'est épargné pour attirer aux consultations les mères de tous les enfants sans exception domiciliées dans l'arrondissement.

A noter surtout, parmi les fonctions des dispensaires ou consultations pour enfants:

1. *La prévention des maladies chez les enfants bien portants*, c'est-à-dire la surveillance régulière du développement de leurs forces physiques et psycho-motrices et la prophylaxie des affections qui pourraient les menacer (vaccination contre la petite vérole, inoculation contre la diphtérie, prophylaxie précoce du rachitisme, etc.).

2. *La surveillance régulière de l'alimentation des jeunes enfants.* Les dispensaires recommandent autant que possible l'allaitement de l'enfant par la mère, prennent toutes les mesures pour assurer une lactation abondante chez celle-ci; le lait des mères dont la lactation est surabondante est recueilli et dispensé, pendant les premiers mois de leur vie, aux nourrissons manquant totalement de lait ou qui n'en reçoivent pas assez de leurs mères. Quand le nourrisson commence à recevoir une nourriture supplémentaire, le médecin du dispensaire lui prescrit les produits lactés, gruaux, sucs vitaminés et autres éléments nutritifs nécessaires, qui sont fournis par la cuisine-fabrique pour enfants desservant le dispensaire.

3. *Le traitement des enfants malades au dispensaire et à domicile.* Chaque enfant malade est traité pendant ses maladies par le médecin qui le surveille quand il est en bonne santé; de même, il est soigné, bien portant ou malade, toujours par la même infirmière diplômée chargée d'exécuter les ordres du médecin. S'il y a lieu, le petit malade est examiné par un spécialiste — laryngologue, oculiste, phthisiatre, chirurgien, etc.; si son état exige l'hospitalisation — le dispensaire le fait transporter dans un hôpital pour

enfants. Si l'enfant a une maladie contagieuse, le médecin pédiatre de l'arrondissement, attaché au dispensaire, en informe l'épidémiologiste de l'arrondissement afin que celui-ci prenne les mesures épidémiologiques nécessaires.

Il va de soi qu'au dispensaire l'examen des enfants malades et des enfants sains est fait séparément.

De plus, les consultations pour enfants fournissent un grand travail culturel. C'est à l'infirmière-visiteuse qu'incombe ici le rôle principal. L'infirmière-visiteuse est chargée de surveiller un certain nombre d'enfants qu'elle visite à domicile. Elle doit connaître à fond non seulement ses petits pupilles, mais aussi leur familles, le train de vie de celles-ci, etc. Elle devient ainsi vraiment l'amie et la conseillère des mères.

Le médecin et l'infirmière-visiteuse prêtent de même assistance à la mère pour tout ce qui a rapport à l'éducation de l'enfant.

Près des dispensaires il y a encore des *bureaux de consultation* sur les questions de droit social qui indiquent à la mère, s'il y a lieu, les moyens de revendiquer ses droits et ceux de son enfant. Ces bureaux s'abouchent avec les organisations sociales et syndicales.

En outre, les dispensaires ou consultations pour enfants jouent le rôle de *centre d'instruction méthodique* pour le personnel de tous les établissements pour jeunes enfants situés dans le même district ou arrondissement.

Les crèches sont des établissements où sont élevés les enfants jusqu'à trois ans, ce qui permet aux mères de travailler et de participer à la vie sociale et politique. On y admet les enfants de 1 mois à 3 ans. Ils sont ensuite répartis, selon leur âge, en groupes comprenant de 15 à 20 bébés. Chacun de ces groupes suit — pour ce qui est de la sieste, des promenades, de la diète, de l'éducation — un régime approprié à l'âge des enfants qui le composent; il y a une infirmière diplômée qui remplit les fonctions d'institutrice et une infirmière non-diplômée (une bonne) pour chaque groupe. Ce personnel est dirigé par la directrice, le pédiatre de la crèche et un pédagogue instructeur qui veillent au développement moral et physique des enfants, à leur santé, à leur alimentation, à leur instruction, à la prévention et au traitement de leurs maladies.

Les jeunes enfants sont admis dans les crèches situées près du domicile de leur mère ou bien desservant l'usine, la fabrique ou le bureau où celle-ci est employée, ce qui lui permet d'allaiter le nourrisson tout en travaillant, pendant les intervalles d'une demi-heure chacun qui lui sont accordés à cet effet par la loi. Les bébés au-dessus de 12 mois sont généralement placés dans des crèches à portée du domicile de leur mère.

Le séjour des enfants à la crèche dépend des heures de travail et des conditions de la vie de la mère. Il y a des groupes qui y passent 8—10 heures de la journée, il y en a qui y restent 12—13 heures, et enfin des enfants qu'on y garde jour et nuit et donc les mères ne les reprennent chez elles que leur jour de sortie.

Le régime diffère pour les enfants malades, c'est-à-dire mal nourris, atteints d'une colite chronique ou de la coqueluche; ceux-ci font partie des «groupes différenciés», reçoivent une diète spéciale et subissent un traitement approprié. Pour les enfants tuberculeux il existe des crèches-sanatoria avec suralimentation et régime approprié.

Pour les tout petits orphelins il y a des «Maisons pour les nourrissons» dont les élèves sont à la charge de l'Etat. Un régime de vie régulier, une alimentation et éducation appropriées garantissent le développement normal de ces enfants.

Pour ce qui est des enfants au-dessus de 3 ans nombre d'établissements veillent à leur santé: ambulances, polycliniques, hôpitaux, sanatoria, écoles-sanatoria ou «écoles forestières», etc. Ici, de même, la plus grande importance est accordée à la prophylaxie des maladies infantiles; on s'efforce de créer une ambiance optimale pour le développement harmonieux des forces physiques, psychiques et morales de l'enfant. Nous possédons un réseau étendu d'écoles maternelles (ou «jardins d'enfants») pour les enfants de 3 à 6 ans; dès 7 ans les enfants sont obligés, selon la loi, d'aller à l'école. Les médecins des écoles maternelles, et primaires répondent de l'état sanitaire et hygiénique de celles-ci, surveillent le développement physique des élèves, leur donnent des soins en cas de maladie, pratiquent les vaccinations prophylactiques, désignent les enfants qui doivent être placés dans un sanatorium, etc. Ces

pédiatres exercent leurs fonctions de concert avec l'ambulance ou polyclinique pour enfants de leur arrondissement ou district.

Les ambulances et les polycliniques pour enfants sont des établissements médico-prophylactiques où les élèves des écoles maternelles et primaires sont soignés par des spécialistes qui, s'il y a lieu, leur font des visites à domicile. Les polycliniques sont dotées d'appareils de radiologie, de laboratoires pour analyses de tous genres, de services de physio-thérapie et autres.

Chaque polyclinique dessert les enfants habitant l'arrondissement (dans les villes, cités ouvrières etc.) auquel elle est affectée. Chacun des médecins de la polyclinique est affecté à un rayon où il fait des visites à domicile; une infirmière diplômée lui est adjointe. De cette façon le médecin et l'infirmière apprennent à connaître à fond les enfants qui habitent leur rayon, surtout ceux qui font de fréquentes et longues maladies, ceux dont la santé est affaiblie, ceux qui sont atteints de la tuberculose, etc. Note particulière est prise de ces enfants; il existe à la polyclinique des salles de consultation spéciales pour eux, par exemple, pour les rhumatisants, les tuberculeux, etc.; ce sont eux qui sont envoyés les premiers aux eaux, aux sanatoria, dans les «écoles forestières» et autres établissements de ce genre.

Très souvent le médecin de rayon de la polyclinique cumule ces fonctions avec celles de pédiatre de l'école maternelle ou primaire locale, ce qui lui permet de poursuivre encore plus efficacement son oeuvre de cure et de prophylaxie.

Les médecins des établissements pour enfants, de concert avec la polyclinique locale, organisent des examens en masse des enfants pour déceler l'helminthiose et l'infection tuberculeuse latentes, pratiquent l'immunisation en masse, le traitement des dents et désignent les enfants à expédier aux sanatoria et villes d'eaux.

Pour le traitement des maladies infantiles il existe un vaste réseau d'hôpitaux: hôpitaux pour les maladies somatiques (non infectieuses), hôpitaux pour les maladies infectieuses et enfin hôpitaux spécialisés (pour les tuberculeux, pour les maladies de la peau, etc.); là où manquent les hôpitaux pour enfants il y a des services ou des salles réservées aux enfants dans les hôpitaux pour

adultes. A peu près 25 ou 30 p. 100 de tous les lits pour enfants sont réservés aux tout jeunes enfants.

Les polycliniques et les hôpitaux pour enfants se concertent pour assurer le traitement ininterrompu et consécutif des petits malades.

L'Union Soviétique possède un grand nombre de sanatoria pour enfants de divers âges: 1° pour les tout petits, au dessous de 3 ans, 2° pour ceux de la période pré-scolaire (3—8 ans) et enfin 3° pour les élèves des écoles primaires et secondaires. Il existe des sanatoria non-spécialisés, c'est-à-dire pour les enfants dont l'état général laisse à désirer — faibles, anémiques, nerveux, etc., et des sanatoria spécialisés — pour les tuberculeux et les rhumatisants. Certains de ces établissements ne desservent que les enfants d'une certaine ville ou d'un certain arrondissement, d'autres les jeunes citoyens d'une seule république; les troisièmes enfin, d'importance fédérale, admettent les enfants de toutes les parties de l'Union Soviétique.

Deux facteurs jouent un rôle important dans la protection de la santé des enfants en URSS: *la vie en plein air pendant les vacances d'été et les exercices physiques.*

Des centaines de milliers d'enfants quittent les villes qu'ils habitent pour passer leurs vacances d'été dans les environs, à l'air, au sein de la nature, et profiter ainsi de leur mieux des facteurs curatifs naturels pour rétablir leur santé. Les crèches et les écoles maternelles («jardins d'enfants») expédient les groupes des «grands» avec leurs institutrices à la campagne, dans les villas qui leur sont allouées; les élèves des écoles s'en vont dans les camps de pionniers. Le régime et l'alimentation y dépendent de l'âge des enfants, qui y prennent des bains d'air et de soleil, se baignent dans les nappes et cours d'eau naturel du voisinage, font des excursions, du sport, des exercices physiques, jouent aux jeux d'ensemble, etc.

Pour les enfants qui sont obligés de rester en ville, on organise des préaux pour jeux près des crèches, des écoles et des grandes maisons à population nombreuse.

En URSS on veille surtout à la bonne organisation des exercices physiques et sportifs.

Chaque matin, avant les leçons, les élèves des écoles font un

temps de gymnastique (10—15 minutes); il y a, de plus, des leçons de gymnastique et des cercles de culture physique et de sport dans les écoles, détachements de pionniers, palais et maisons pour pionniers et écoliers; tels sont les moyens qui assurent la participation en masse de nos enfants aux exercices physiques et aux sports.

La chaire que je dirige à l'Institut des médecins pédiatres à Leningrad a élaboré un système de massage et de gymnastique pour les tout petits enfants, à partir du 4^e ou 5^e mois de leur vie, — système qui a été employé avec succès. Cette méthode, ainsi que l'a démontrée notre expérience et celle de nos collègues en URSS, constitue un excellent moyen de stimuler le développement harmonieux de l'enfant; on ne saurait trop la recommander aux établissements pour enfants, car elle constitue la meilleure des mesures prophylactiques pour éviter l'hospitalisme.

C'est aux institutions du Ministère de la Santé Publique de l'Union Soviétique et de ceux des Républiques Fédérées qu'incombe la tâche d'élaborer et de mettre en œuvre, de concert avec les Ministères de l'Instruction Publique, les mesures nécessaires pour la protection de la santé des enfants. Dans les établissements pour la cure et la prévention des maladies infantiles on se préoccupe aussi de l'éducation et de l'instruction des enfants malades et bien portants.

La protection de la santé des enfants de tous les âges, organisée par notre gouvernement sur une grande échelle, exige un grand nombre de médecins-pédiatres et d'infirmières diplômées ayant reçu un enseignement spécial qui les rend aptes à soigner les enfants.

Les médecins pédiatres se recrutent parmi les étudiants des instituts de médecine qui se sont spécialisés dans la pédiatrie; en outre, ils sont formés par des facultés de pédiatrie spéciales près les instituts de médecine; Leningrad possède l'institut des Médecins Pédiatres, consacré à cette branche de la médecine. Les étudiants de celui-ci, de même que ceux des facultés de pédiatrie des instituts de médecine, reçoivent l'enseignement habituel de rigueur pour les étudiants en médecine, avec cette différence toutefois qu'ils étudient de la façon la plus détaillée, pendant tout le

cours de leurs études, l'anatomie, la Physiologie et la pathologie infantiles.

Les étudiants en médecine des dernières années suivent des cours non seulement dans les cliniques pour adultes, mais aussi dans les cliniques pour enfants, où ils étudient les maladies infantiles de tous les types — somatiques, infectieuses, chirurgicales, les maladies de l'oreille, des yeux, etc. De cette façon ils peuvent se spécialiser dans la pédiatrie au cours de leurs études.

L'élaboration de nouvelles mesures pour la protection de la santé des enfants exige des *recherches scientifiques*, dont s'occupent les chaires de pédiatrie, les instituts de recherches scientifiques spécialisés, les hôpitaux pour enfants et autres institutions.

Tels sont les moyens employés en URSS pour la protection de la santé des enfants, qui, chez nous, est véritablement une œuvre nationale. Qu'elle atteigne des proportions grandioses — c'est ce dont témoignent les sommes assignées au budget de l'état pour l'assistance de l'enfance, ainsi que l'accroissement énorme des établissements pour la cure et la prophylaxie des maladies infantiles durant les années de gouvernement soviétique. Les résultats de ce travail se font sentir par la forte diminution des maladies et de la mortalité des enfants.

La Constitution Stalinienne de notre Union, les lois historiques du 27 juin 1936 et du 4 juillet 1944, ainsi que la part active que prend le peuple entier à la protection de la santé des enfants sont le gage de nouveaux succès dans la lutte pour la vie et la santé des petits citoyens soviétiques et la garantie d'un avenir heureux pour notre Grand Pays.

Result of a Systematic Health Program for Mothers and Children in Oslo.

By **Kirsten Utheim Toverud, M. D.**

Chief of the Municipal Health Centre for Mother and Child in Oslo.

In Norway preventive Pediatrics has been performed partly by the public school Health department and partly in the infant welfare centre by private Health organizations. Both kinds of

work has mostly been limited to the cities and industrial districts. In the rural districts very little preventive Pediatrics has been done.

In 1937 the Norwegian Pediatrics Society asked the Government to support the private Health organizations in their effort to supervise the infants. At the same time the Society sent a request that the Infant welfare centres ought to extend their supervision to the complete 1st growth period of life, that is: fetal life, infancy and preschool age.

When the public dental service for the preschool age group started in Oslo 1938 a systematic Health program for the 1st growth period was included in the plan for the Northern East part of the city, which covers a population of about 70 000 inhabitants. This Health program was regarded as a scientific experiment in order to see to what extent prevention of dental caries in the preschool age period might be achieved by close supervision of the pregnant women, infants and preschool age children. The program included monthly and during the last month weekly visits during pregnancy to the Health centre, monthly visits during infancy and visits 4 times a year during preschool age. Besides a routine physical examination, urine analyses, hemoglobin and during the war ascorbic acid determinations of the blood were performed at least once a year in the children and if possible each month during pregnancy. Tuberculin tests were performed twice yearly to all those visiting the Health Station and X-ray examination of the chest of the positively reacting ones.

During the war the blood calcium and the vitamin B₁ excretion in the urine of the pregnant women were followed as well. Demonstrations in food preparations were given at the Centre once or twice weekly by a nutritionist and demonstrations in physical training by a physiotherapist. Lectures in mental hygiene were included in the program.

The diet during pregnancy was made as sufficient as our sources allowed to meet the requirements of the excessive growth period of pregnancy. All pregnant women, infants and preschool age children were given 3/4 L of milk and 5—10 cc of cod liver oil during the whole period of the war. Vitamin K was given during

the 3 last weeks of pregnancy after having studied the effect of this addition on the blood of new born infants finding a lowering in the coagulation time. Cod liver oil was given to all infants from the age of 2 weeks whether breastfed or not in doses of 1—2 teaspoonful — 300—600 units per day. To all premature infants 900 units daily were given during the whole infancy. Reduced iron (0.10 g) was added to the diet of all infants from 4 months of age whenever the hemoglobin was low. To the premature infants however this addition was made from 2 months of age whether the hemoglobin level was low or not and was continued with short intervals throughout the whole period of infancy.

A few results of the health program in progress since 1939 may be of interest.

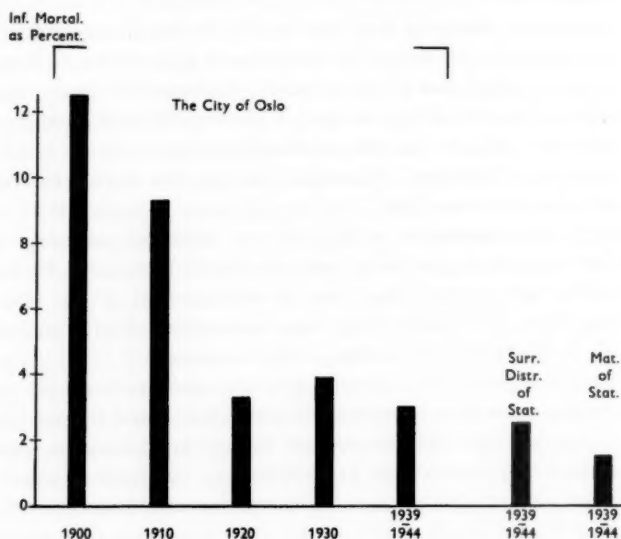
The infant mortality has been low in Norway compared with other countries. The figures for Oslo show a marked decrease from the year of 1900 when it was about 12 %. As is seen from table 1 it decreased to 3 % during the first 5 years the Health Station was at work and to 2.6 % in the surrounding district of the Station. In the group of mothers and infants visiting the Station the total infant mortality was just 1.4 % in the same 5 years. With decreasing total mortality in infancy the neonatal mortality expressed as percentage of total infant mortality has constantly been increasing since 1900 and was in our material of the Health Station 80 %. In about 1 000 cases supervised during prenatal life no intra-cranial hemorrhage has occurred.

As a further effect of the preventive measures in the supervised population a lowering of premature births was found to take place when the mothers were supervised during pregnancy compared with those supervised just after delivery. As table 2 shows a reduction of 52 % was obtained in the premature birth rate. With a mean statistical error of ± 1.05 this difference is statistical significant.

Rickets has been very rare in the material of the Station. A slight osteoporotic condition in the form of an early cranio tabes and slight bowing of the legs round 1 and 1 $\frac{1}{2}$ years of age has been present in the group for the last 3 years, in just 1 % of the

TABLE 1. Total infant Mortality of the City of Oslo.

Years		No. of Deaths during 1st Year as Percent of life born Inf.	Neonat. Deaths as Percent. of total infantile Deaths
1900	City of Oslo	12.5	24
1910	" " "	9.3	28
1920	" " "	3.3	44
1930	" " "	3.9	61
1939-44	" " "	3.0	65
1939-44	Surr. Distr. of Health St.	2.5	57
1939-44	Mat. of Health St.....	1.4	80



infants and children till 2 years of age. In premature infants no rickets has occurred. (Table 3).

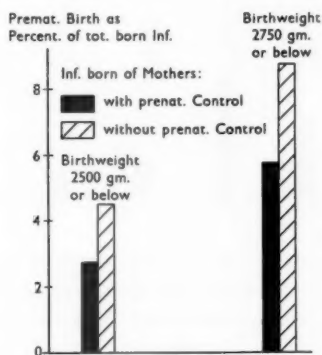
A finding of interest is the increased number of lactating women among those supervised during pregnancy. As is seen from table 4 the difference in the lactating power between mothers supervised

TABLE 2.

Frequency of premature Birth based on Birth Weight: 2 750 g.
1939—45.

Pre- and postnatal. contr. Infants.		Just postnatal. contr. Infants.	
No of Infants		No of Infants	
Exam.	Percentage of premat. born	Exam.	Percentage of premat. born
973	5.8	2 975	8.8

The mean statistical error ± 0.91 .

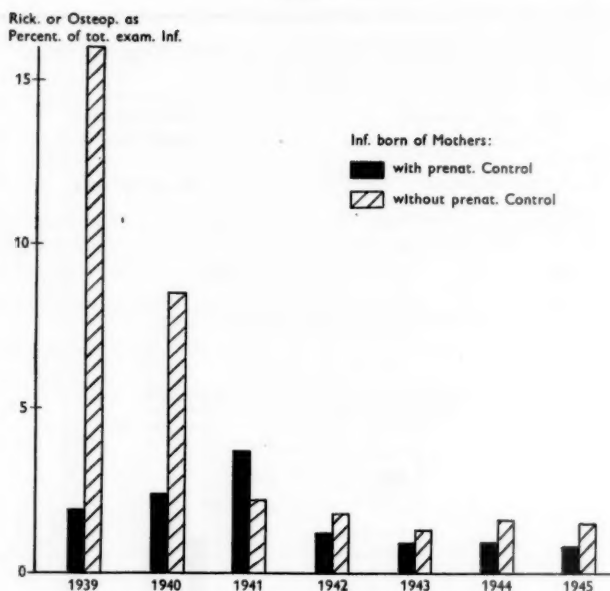


and not supervised during pregnancy was quite marked in the years before the war. During the war the difference was less marked probably on account of no choice of food in general.

Finally the results of the Health program on the prevention of dental caries has to be mentioned.

From 2 years of age all children on the Health station, have been examined by a dentist before the physical examination of the doctor was performed. In this way the doctor was able to make a complete appraisal of the state of health of the child. If an acute caries has taken place since the last visit at the Station it is up to

TABLE 3.



the physician if possible, to find the cause of the development of caries. A marked general decrease took place during War, 83 % reduction. As may be seen from table 5 the incidence of caries has been reduced to 50—60 % in children regularly visiting the Health Station before 1 year of age. The reduction is most marked in the 2 first age groups of children from 2 $\frac{1}{2}$ —4 years of age. A close cooperation of the pedodontist and the pediatrician in this work has been found to be of the greatest benefit.

The result of this Health program during the first period of growth has encouraged still more systematic measures as far as preventive Pediatrics is concerned. We wish now to include the whole period of growth in our health program. There is no reason for separating the public school health program from that for the years before school age. In the period of adolescence there is no preventive health work at all going on in our country. This period

TABLE 4.

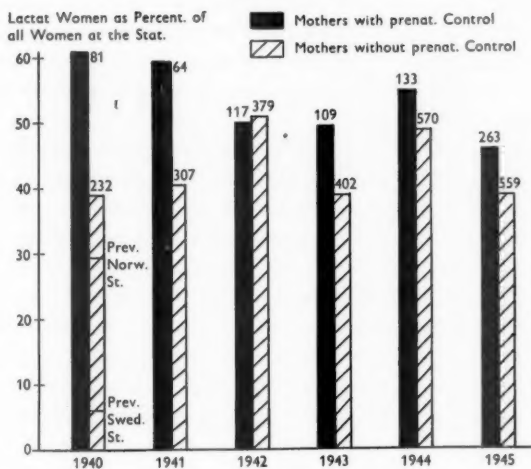
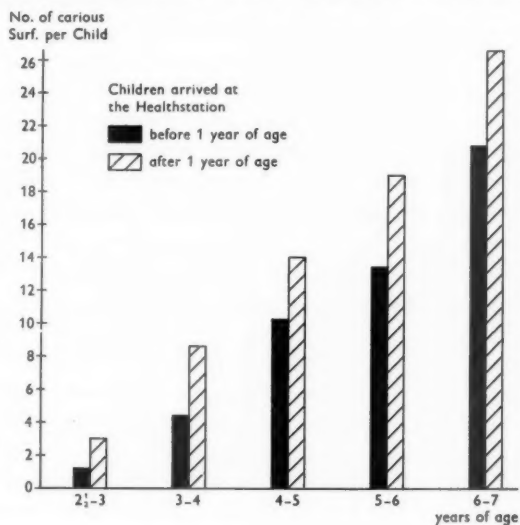


TABLE 5. Dental Caries at the Health Station 1940-1944.



is of particular interest because it is both physically and mentally an unbalanced period with great predisposition to various forms of disease and it is the period just preceding the child bearing age. Much of the health work performed in the previous years will partly be wasted if the prophylaxis is not followed up in these important years of puberty.

During the last winter an official committee of the community surrounding the city of Oslo has made a proposal of, connecting all preventive measures during the whole growth period from fetal life till adult life in one health centre for each part of the population corresponding to 10 000—25 000 inhabitants. This proposal was agreed to by the Municipal council just before I left Norway. These health centres are going to be placed not in the hospitals but in our public schools, gradually as new ones are erected. Separate entrances from the street are of course arranged for the pregnant women, infants, preschool age children and adolescents with separate days for each group. In these centres the physical as well as the mental state of the mothers and children will be supervised by physicians, psychologists, dentists, social workers and health nurses. In this way an individual's whole growth period will come under regular public health supervision with cooperation from all those concerned in the task of securing good health in the individual. In this way we will be able to gather valuable statistical data of great importance for the future.

Thus we fulfil the true democratic idea that, as far as health supervision is concerned, each citizen at the end of the growth period goes out well fitted for working life regardless of his economic status.

The Construction of a Modern Children's Clinic.

New Children's Clinic in Helsinki, Finland.

By Arvo Ylppö, M. D.

Professor of Pediatrics, University of Helsinki, Finland.

The first children's clinic «Hôpital des Enfants Malades» was built in 1802 in Paris and is still working. It had big patient-

rooms as customary also in hospitals for adults. But the results in this hospital as in others built afterwards were not good. Gradually the opinion gained ground, that in these hospitals the children did not die of the diseases from which they were suffering on arriving, but of those they contracted there.

A revolutionary change in the construction of children's hospitals was brought about by Prof. Rauchfuss from Leningrad. He organized a decentralisation and divided the children's hospital into several small pavilions; one for each of the so-called epidemic diseases of children e. g. scarlet fever, diphtheria etc. The great St. Vladimir-Hospital in Moscow was built after his model in 1875. In addition to one large building it contained a number of pavilions.

All the bigger children's hospitals at the end of the last century and at the beginning of the present one were constructed in the same way. But this type of hospitals was very uneconomical and unpractical as many pavilions stood occasionally almost empty for long times, because of the temporary disappearance of the epidemic in question.

Infants were not admitted into the children's hospitals until the beginning of this century. New problems now presented themselves due to the importance of so-called respiratory disturbances, as influenza, coughs and colds by side of the diarrhoea. Their prevention is still more difficult than of so-called acute epidemics of children. This caused the need of special isolated wards in children's hospitals where both infants and bigger children were cared for.

The ideal children's hospitals built in 1910—30 consisted thus of one bigger central hospital and a separate quarantine station for doubtful and clearly infectious cases. But so-called real children's epidemic diseases were no more admitted into the children's hospitals. Special epidemic hospitals with many different pavilions open both to adults and children were built in order to prevent the children's hospital from getting too big and to prevent the spreading of epidemics among the other children.

This division of children's diseases into two different groups: epidemic diseases, which were treated in special hospitals and other diseases may be advisable in very big cities but it has many great

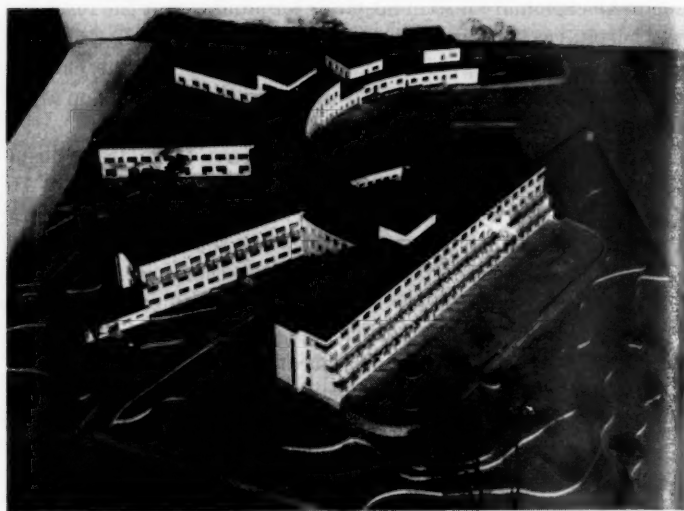


Fig. 1. General view from the Children's Clinic in Helsinki, Finland.

disadvantages. Firstly there is always a possibility of the occurrence of epidemic cases in different wards. If the hospital has not its own epidemic section, these cases must be sent to another hospital. Secondly, the children's hospitals are also the most important schools for the training of children's physicians and nurses in children's diseases.

A children's hospital without an epidemic section of its own is not a good training place. *Prevention and knowledge of epidemic diseases forms an important part in the education of good children's physicians and other nursing-personnel.*

During his training years a young children's physician must learn to know also the *healthy child* and its development and the ways to keep it well. It is possible only if the *clinic is closely combined with a Child Welfare Centre*, where the mothers bring their healthy children from birth to school-age. Under the direction of senior physicians the young ones can learn the physiology and



Fig. 2. Even the small infants are brought in the wintertime out on the balconies, which are in direct connection with patients' rooms.

feeding of the healthy children and prevention of different diseases: in short *social and preventive pediatrics*.

In order to keep well a healthy child needs much *sunshine and fresh air*. For a sick child these are *still more important*. But it is not often that the sick child gets these natural remedies.

During the war and in spite of its difficulties we have built a new children's clinic in Helsinki, Finland. It was opened in the summer of 1946. In building it our leading principles were as follows:

1. We have tried to build a children's hospital with the greatest possibility of *avoiding the spreading of all kinds of infections* — including flu and coughs — from ward to ward and from child to child.



Fig. 3. The Facade in the form of a terrace. Bigger children in lower stories, small infants higher.

2. We have tried to give every infant and child opportunity to get *fresh air by combining the wardrooms directly with open balconies.*

3. We have tried to organize a *training school*, where future physicians and special nurses for children can become acquainted with *all kinds of children's diseases*, epidemic diseases included and *with the methods of care for premature and other children.*

In its capacity both as hospital and university training school the clinic has altogether 13 different wards. They are grouped as follows:

1. a ward for *premature children* and the *healthy children of the wetnurses.*

About 10 % of all children in Finland are born prematurely i. e. weighing less than 2 500 g (5.5 lb.). The mortality among them is extraordinarily high amounting in some years to 50 % during the first year. The mortality of these children increases considerably the general infant mortality. This is why all phy-

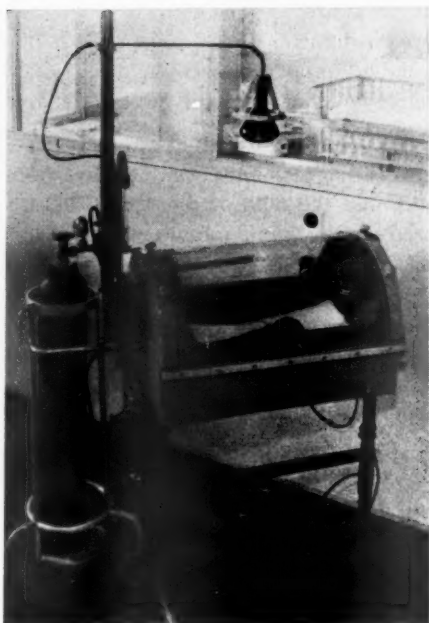


Fig. 4. Incubator for premature children.

sicians must learn the different methods in care of premature children.

2. wards for other infants.
3. wards for children in play- and school-age.
4. quarantine station for children with doubtful diagnosis and with acute respiratory and intestinal disturbances.
5. surgical wards for infants and children.

In addition to surgical treatment an infant must have special care from persons with pediatric training; otherwise the results may be quite unsatisfactory.

6. a special epidemic ward, which receives children with all kinds of epidemic diseases from different wards as well as from outside the hospital.

7. out-patients ward.
8. child welfare centre.
9. X-ray, laboratories, massage- and physical-treatment.
10. the milk- and diet-kitchens for children.
11. the mothermilk centre.

This gathers the surplus milk from healthy mothers from outside. This milk and the milk of the wetnurses, who live in the hospital, is used for the young infants with serious intestinal and alimentary disturbances.

The number of beds is 350. The exterior of the hospital resembles a *hand with spread fingers*. This strange form results from our attempt to combine the old pavilion and block-system. *Each finger can function as an independent hospital.* But it is easy to reach from there the laboratories and the administrative apartments in the curved central part of the building.

It would be difficult and inconvenient in our cold climate to transport small patients to laboratory and to X-ray investigations from dispersed pavilions. Separate pavilions prove much more expensive to build and use.

The clinic is only 1—4 stories high. The use of a lift involves many dangers in childrens hospital, for which reason we have given up the high blockbuilding, the usual type of hospitalbuilding in present times. In addition to this the infections have the tendency to spread more easily in high buildings than low.

This kind of divided building has proved advantageous with regard to prevention of infections inside the hospital. For the same purpose the patients' rooms are small. Every ward has several rooms for 1—2 children, and the greatest number of patients per one room is 6.

The glass walls between the rooms enable the nurse to inspect simultaneously the patients of several rooms as well as the work of probationers.

The facade in form of a terrace is due to our desire to give *every infant and child opportunity to be brought directly from the patients' room to the balconies into the fresh air.* This terrace-system has as a result that the rooms in lower stories are deeper and bigger than



Fig. 5. A special bed for smallest infants, which can be covered with a net against the flies and too much sun without however, preventing the child from getting enough fresh air.

in the higher. But it is very suitable just in a children's hospital, as the same number of bigger children placed in the lower stories need more floor area than the small children and infants in the higher stories. From the lowest story the biggest children can get easily straight into the yard.

The question of ventilation in children's hospitals is a very difficult one. We have solved the problem so that the spoiled air is sucked away from the patients' rooms and the fresh air is compressed heated into the corridors, from where the overpressure makes it spread to both sides.

Besides the arrangements for the search and alarm of the personnel we have microphones in patients' rooms connected with a receiver apparatus in the room of the nurse on duty. This is of special importance during the night. One nurse can control every noise or voice in different rooms easily by turning a searcher-switch.

As revealed in the above our clinic has consistently tried to follow the principle that *the children's clinic with its specialised doctors and nurses is the place where primarily must be concentrated every kind of care for sick infants and children*, this including internal, psychological, surgical and epidemiological treatment. In addition to these, different *institutions for preventive pediatrics* such as *child-welfare and mothermilk-centres* must be combined with the work of a modern children's clinic.

Section 3—Bio-Immunological Procedures.

Immunization against Diphtheria in Newborn Babies and in Infants.

By **Bo Vahlquist**, Stockholm, Sweden.

The results from recent years of Schick tests and antitoxin determinations in the blood clearly demonstrate that the situation in regards to *natural* immunity against diphtheria nowadays is most unsatisfactory in many countries of Europe. In Sweden the number of Schick negative individuals among non-immunized adults does not exceed 10 per cent. As a consequence the newborns only infrequently demonstrate that passive immunity, which was formerly assumed to be the rule. The question of immunization already at an early age therefore becomes topic. Earlier authors almost unanimously expressed the view that an immunization during the first months of life is not practicable, the infants at this age being considered to have a poor antitoxin producing power. The results of experiments, which will be published in detail in a following number of this journal, clearly demonstrate that this opinion is erroneous. Even the newborns react upon diphtheria immunization with aluminium precipitated toxoid, although the response in antibody formation is often delayed. Earlier workers seem to have been misled by one or several of the following errors: the slow reaction of the newborns; the more or less complete interference of «passive» antibodies exceeding 1/50—1/10 A. U./cc, with the active immunization; — and the importance of even minute amounts of «active» antibodies, indicating former sensitization, for the results of immunization.

A New Approach to the Problem of Diphtheria.

By **Fr. V. Groër**, M. D., Cracow, Poland.

The active immunization against diphtheria has not solved all problems of diphtheria prophylaxis. We are very often confronted with situations, in which the passive, immediately effective immunization is not to be avoided. This last procedure plays a very important role in countries, where the great majority of small children is organized in creches and kindergarten institutions.

The passive immunization with horse, or even sheep serum leads to sensibilization, even the new highly purified globulin gamma sera are not absolutely free from this very disagreeable property. It is not necessary to emphasize what this means in cases of repeated prophylactic or therapeutic administration of serum. It would be therefore very important to obtain a serum absolutely free from allergenic properties. Such a serum can only be the human serum.

The idea of using human antitoxic serum for diphtheria prophylaxis is probably not new, but it has never been realized for the following reasons:

1. Because of the difficulty of collecting a sufficient amount of human serum.
2. Because according to literature the titre of the human antitoxic serum is very low and can hardly be brought to a sufficient level.

These two difficulties can be actually considered as already overcome.

War has taught us that collecting large quantities of human blood for transfusion purposes and for preparation of plasma is not at all so difficult. The importance of human blood and plasma for modern treatment is so great, that even after the war this procedure has been continued. In Soviet Russia huge establishments for collecting human blood were in existence already before the war for two purposes: First as blood transfusion centres, where collected blood was preserved and distributed and secondly, as centres for collecting serum for the prophylaxis of measles. The

question of collecting sufficient quantities of human serum is thus only a question of organization.

The potential ability of producing diphtheria antitoxin is the rule among humanity. Only about 16 % of all adults are not capable of producing antitoxin. It is true, that the natural level of the antitoxin content in blood of adults is not very high and varies between 0.01—0.2 A. U., occasionally over 0.2 A. U. pro 1 cc. But — by means of selection and proper methods of immunization this titre can be considerably raised.

Such experiments have been carried out under my supervision in Lvov in the Sanitary Bacteriological Research Institute (Prof. Tchornaya) and the State Research Institute for Maternity and Child Welfare (Prof. Groër) 1945/46 by my co-workers Stepanidova and Kogan, using the local Measle Prophylactic Centre as a basis.

The donors of this centre (in average 23 years old) were first of all Schick-tested. All positive individuals were eliminated. In Schick negative individuals Jensen-titration of serum was carried out and all individuals with antitoxin content below 0.02 A. U. were again eliminated. The rest, divided into three different groups, underwent an active immunization with Diphtheria Anatoxin from the Metchnikoff Institute in Moscow (1 cc — 40 I. U.). The best results were obtained by means of 5 injections after the following scheme:

40	20	10	5	5	Imm.	Units.
13	30	10	11		Days	(intervals).

To our great astonishment we obtained sera which contained from 125 to over 250 A. U. in 1 cc. This titre was maintained still 40 days after the last immunization and had rather a tendency to rise.

It was thus possible to collect mixed sera with a titre of over 125 A. U. in 1 cc which have proved their full prophylactic and therapeutic value in experiments on animals and children.

These sera may be used not only for prophylactic but also for therapeutic purposes. But it is of course possible to concentrate them. They are not so easily eliminated from the organism and we had the impression that they are even more efficient, which is probably due to the fact, that they are more easily resorbed.

Une nouvelle réaction pour la recherche de sujets réceptifs à la diphtérie; la voie percutanée pour l'immunisation chez les animaux de laboratoire.

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La réceptivité des sujets à la diphtérie est déterminée, à l'heure actuelle, par deux épreuves devenues classiques: la réaction de Schick et la réaction de Réh.

Rappelons que la première consiste à introduire dans l'épaisseur du derme une petite quantité de toxine diphtérique correspondant au 50ème de la dose minima mortelle pour un cobaye de 250 grs. Si la quantité d'antitoxine du sang circulant est nulle ou inférieure à 1/30ème d'unité par cm 3, la réaction au niveau du point d'inoculation se traduit par une rougeur avec infiltration légère, qui apparaît 24 à 48 heures après l'injection, atteint son maximum au bout de 4 à 5 jours et persiste pendant 10 à 12 jours. Puis le phénomène local s'efface peu à peu, en sorte qu'après une desquamation légère il ne subsiste plus qu'une pigmentation d'intensité et de durée variables.

Lorsque le sérum contient au moins 1/30ème d'unité antitoxique par cm 3, l'introduction de toxine n'est suivie d'aucune modification au point d'injection: la réaction est négative. En pratique, un tel sujet peut être considéré comme réfractaire à la diphtérie (Schick, Park et Zingher, Bundesen, Ramon et Debré).

Pour obtenir la réaction de Réh, on dépose sur une scarification de la peau une gouttelette de toxine diphtérique titrant 30 unités antigéniques. On laisse sécher à l'air. Chez les sujets réceptifs, après 24 à 48 heures, une zone d'hyperémie de 3 à 15 mm de diamètre se dessine autour du point scarifié. Elle est circulaire à contour net, et accompagnée d'une infiltration sous-jacente plus ou moins manifeste. Le plus souvent le centre de cette tache rouge montre une petite vésicule. La réaction atteint son intensité maxima du 2e au 3e jour; elle pâlit ensuite pour disparaître du 8e au 15e jour, laissant parfois après elle une légère desquamation. C'est au 3e jour que la réaction est la plus nette.

L'une et l'autre de ces épreuves doivent être contrôlées par un témoin à la toxine chauffée.

Dans la pratique médicale journalière, la réaction de Schick est délicate: 1° — Il faut préparer extemporanément la dilution de toxine. 2° — L'intra-dermo-réaction est douloureuse et pour cette raison les enfants s'y prêtent difficilement.

La méthode de Réh est d'une application plus facile; cependant, elle exige également quelques précautions: il faut laisser sécher la gouttelette de toxine, desiccation relativement lente même lorsque la toxine est incorporée à de la glycérine (minimum 10 minutes) (Nelis et Vandenhouten — Ruelle et Maryssael).

Par ailleurs, il est nécessaire d'obtenir l'immobilité des jeunes enfants pendant ce temps; on doit les surveiller individuellement, ce qui, lorsque l'on pratique le contrôle en série, est parfois difficile.

Nous avons pu mettre au point une nouvelle réaction dans laquelle les inconvénients de ces deux épreuves sont éliminés.

Elle consiste en une simple friction de la peau à l'aide d'un mélange de toxine diphtérique d'un pouvoir antigénique élevé et de glycérine, celle-ci facilitant la pénétration de certaines substances dans le derme. (Renaux et Maryssael).

Nous avons communiqué notre plan de travail au Professeur Renaux, qui nous encouragea dans nos recherches.

Celles-ci furent effectuées principalement sur le lapin, dont la sensibilité à la toxine diphtérique est bien connue.

Une toxine titrant 41 unités antigéniques et 500 doses mortelles au cc, fut mise obligeamment à notre disposition par le Professeur Paul Bordet, Directeur de l'Institut Pasteur de Bruxelles.

La résorption de la toxine diphtérique par la peau peut être facilement démontrée par l'expérience suivante:

Le 26 août 1946, nous pratiquons sur le ventre d'un cobaye de 300 grs une friction légère au moyen d'une goutte du mélange de deux parties de toxine, titrant 41 unités, et d'une partie de glycérine. Le titre du mélange est donc ramené à 27—28 unités. La peau a été, au préalable, légèrement irritée par une friction à l'alcool. (Les essais ultérieurs montrent que cette irritation n'est nullement nécessaire chez le lapin.)

L'épreuve de Réh est pratiquée en même temps et symétriquement avec le même mélange.

Le 27: la réaction de Réh est négative, tandis que la région soumise

à la friction montre une infiltration nette de la peau. L'animal en expérience a perdu tout appétit, l'état général est manifestement mauvais.

Le 28: Réaction de Réh: positive.

Nouvelle réaction: très grosse infiltration.

Les 29, 30 et 31 la réaction de Réh évolue avec l'aspect classique.

Au niveau de la nouvelle réaction: le 29 léger suintement sur l'infiltration.

Le 30: noircissement de la peau.

Le 31: eschare noire. L'état général semble meilleur; cependant le 1^{er} Septembre, c'est-à-dire 5 jours après l'expérience, le cobaye meurt. L'autopsie n'a pas été faite par suite de circonstances indépendantes de notre volonté.

Entretiens, le 28 août, nous avons procédé à la même expérience chez un lapin.

Le 29: Réaction du Réh: négative.

Nouvelle réaction: érythème avec infiltration de la peau et suintement léger. Le lapin ne mange pas, son état général est mauvais.

Le 30: la réaction de Réh est devenue positive, tandis que s'accroissent les manifestations déclenchées au niveau de la nouvelle réaction.

40 heures environ après le début de l'expérience, l'animal succombe.

A la nécropsie: dans la zone de la nouvelle réaction, congestion veineuse du péritoine sur une superficie d'environ 5×7 cm; pas de liquide dans la cavité abdominale; les surrénales sont rouges et turgescents, le myocarde mou.

Un deuxième lapin et trois autres cobayes ont succombé à l'application du mélange toxine-glycérine (20 ou 28 u.) après simple dégraissage de la peau à l'éther.

Une première conclusion s'impose: *La resorption de la toxine diphthérique par la peau peut être suffisante pour provoquer la mort.*

Il convenait de rechercher dans quelles proportions le mélange de toxine et de glycérine devait être fait pour indiquer la sensibilité du lapin à la toxine sans toutefois déterminer d'autre phénomène qu'une réaction locale.

La toxine diluée dans deux volumes de glycérine et titrant donc 13—14 unités provoque encore une énorme infiltration avec eschare profonde.

Par contre, la toxine à 6 1/2—7 unités ne détermine que des phénomènes locaux peu accentués et irréguliers.

Un mélange titrant 9—10 unités et ayant un PH 7—7 1/2 s'est révélé le plus favorable à la pratique de la nouvelle réaction chez le lapin.

Voici la technique employée:

On nettoie la peau à l'éther, on y dépose, à l'aide d'une pipette Pasteur, une gouttelette (plus ou moins 0.03 cm³) qu'on étend par friction douce sur une superficie de 1.5 cm sur 3 cm environ. Pour éviter la pénétration de la toxine chez l'opérateur, celui-ci se protège le doigt à l'aide d'un doigtier en caoutchouc.

Une friction de 5 secondes est en général suffisante pour la résorption cutanée, mais elle peut être prolongée sans inconvénient s'il y a lieu.

Au cours des 24 heures qui suivent apparaît, à l'endroit de la friction, un érythème accompagné d'une légère infiltration de la peau. Dans la suite, il se forme, sur cet érythème, une petite croûte jaunâtre qui tombe après quelques jours (4e à 20e) laissant une peau intacte.

L'état général du lapin n'est jamais affecté par cette réaction, il continue à manger et à grossir, demeure aussi alerte qu'à l'ordinaire.

Nos expériences ont porté, jusqu'à présent, sur 35 lapins, avec des résultats constants, si le mélange toxine-glycérine titre 9—10 unités antigéniques.

La préparation reste active plusieurs mois à condition que le PH soit voisin de 7—7 1/2. Ainsi, l'activité d'une préparation datant de 9 mois et maintenue à la température de 15° à 20°, s'est parfaitement conservée.

Des contrôles à la toxine chauffée ont été pratiqués simultanément et symétriquement chez les animaux en expérience: sauf un érythème léger et fugace, mais sans suintement, dans un seul cas, toutes les épreuves de contrôle sont restées négatives.

Notons que la nouvelle réaction s'est toujours montrée plus précoce que la réaction de Réh.

Il était légitime de songer à rechercher la possibilité *d'appliquer en pédiâtrie les notions acquises au laboratoire.*

Nous avons fait nos recherches cliniques dans le service du Dr Henry, que nous tenons à remercier.

Voici la technique de la nouvelle réaction: après avoir provoqué un érythème de la peau par nettoyage à l'éther ou à l'alcool, nous avons déposé sur le bras, au niveau du deltoïde, au moyen d'une

pipette Pasteur, une gouttelette d'un mélange de toxine-glycérine.

Nous l'avons fait pénétrer par friction avec l'index protégé à l'aide d'un doigtier en caoutchouc, la friction portant sur une surface d'environ 1 cm².

Nous avons trouvé commode d'employer le petit doigtier rugueux qu'utilisent les employés de banque pour compter les billets, sa meilleure adhérence à la peau, permettant de faire pénétrer plus facilement le produit et de limiter la surface de la friction.

Celle-ci doit être superficielle, tout en provoquant un érythème momentané; quelques secondes suffisent.

Il faut limiter la friction et ne pas érafler la peau, de façon à éviter une trop forte réaction.

Avec la toxine que nous avons utilisée, le mélange glycérimé favorable à la pratique de la réaction est celui titrant 18 unités antigéniques et ayant un PH 7—7 1/2. Le titre de la dilution à utiliser devra peut-être, être exprimé en doses minima mortelles; il se peut, en effet, qu'une toxine renfermant le même nombre d'unités antigéniques que celle que nous avons utilisée, mais contenant un nombre plus élevé de doses minima mortelles, donne des réactions trop vives.

Quelques heures après la friction (3 à 4 heures environ) apparaît, un érythème avec infiltration plus ou moins marquée.

Parfois cet érythème est accompagné de petites papules rouges qui peuvent être ecchymotiques.

Dans certains cas, la réaction ne dépasse pas le stade érythème-infiltration; dans d'autres, elle se recouvre en son centre d'une petite croûte humide jaune-grisâtre, ou brun-rouge, qui sèche et tombe au bout de quelques jours, sans laisser de cicatrice.

Le maximum de la réaction est atteint au bout de 24 à 48 heures; il y a un statu-quo des lésions durant 2 à 3 jours, puis les phénomènes régressent.

La réaction est indolore, même lorsqu'elle est très marquée; elle n'influence jamais l'état général.

Nous avons toujours pratiqué simultanément le Réh avec le

mélange toxine-glycérine titrant 28 ou 30 unités, et notre réaction avec le mélange titrant 18 unités.

Il faut évidemment toujours faire une réaction contrôle avec de la toxine chauffée.

Nous avons choisi comme point de comparaison la réaction de Réh, parce qu'il résulte d'un travail fait par Régamey en 1943 à l'Institut de bactériologie de Berne et basé sur le dosage de l'anti-toxine diphtérique dans le sérum que le test de Réh se révèle beaucoup plus sévère que celui de Schick.

Il ressort également de ce travail que 3 % des patients testés au Réh et 10 % de ceux testés au Schick sont négatifs sans jouir d'une immunité humorale suffisante.

En nous basant sur ces deux tests cutanés, nous vaccinons donc trop peu d'individus réceptifs.

Jusqu'à présent, notre réaction a été positive chaque fois que le Réh était positif et assez souvent lors d'un Réh négatif; ce qui semblerait indiquer qu'une percutiréaction négative exige une immunité plus solide qu'une cutiréaction négative.

Nous pratiquons actuellement les dosages de la valeur antitoxique du sérum des cas étudiés, mais c'est un travail très long et nous n'en avons, jusqu'à présent, pas fait assez pour établir une statistique.

Il n'y a pas toujours de parallélisme entre l'intensité des cuti et percutiréactions. Il peut y avoir un Réh très peu marqué avec une nouvelle réaction très forte et réciproquement.

Voici les avantages de cette réaction:

- 1° — Beaucoup plus précoce.
- 2° — Plus sensible.
- 3° — Elle est facilement admise par les enfants.
- 4° — Elle est d'une application plus aisée; dès que la réaction est pratiquée, on peut laisser l'enfant sans surveillance, ce qui permet de faire les réactions en série, sans perte de temps.
- 5° — Enfin, cette réaction est en même temps une *amorce de vaccination antidiphtérique*. En effet, nos expériences nous permettent d'affirmer la possibilité d'immuniser les animaux de laboratoire par la voie percutanée.

Voici quelle est notre façon de procéder:

Nous commençons par provoquer une réaction avec le mélange toxine-glycérine titrant 10 unités, réparti sur une surface de 3 à 4 cm² env.

Trois semaines à un mois plus tard, lorsque la peau est redevenue absolument normale, nous pratiquons, en un autre endroit du corps, une friction de même étendue, avec un mélange titrant 14 unités; après disparition de toute trace de cette deuxième réaction, nous refaisons une friction à 14 unités; nous pourrions ensuite sans danger passer à 20 et à 28 unités.

Si la deuxième friction à 14 unités a encore amené une réaction très marquée, il est préférable d'en refaire une troisième avant de passer à la concentration supérieure.

Il est nécessaire de pratiquer toujours au moins 2 fois la friction à 14 unités parce que la première peut amener une réaction minime et la suivante, faite 15 jours à 3 semaines plus tard, une réaction intense, alors que cependant le mélange utilisé titre le même nombre d'unités antigéniques (L VII—XIIX); de même si, après avoir provoqué une réaction violente avec 14 unités, on passe directement à 20 unités, on risque d'amener la mort du lapin par intoxication diphtérique (Cf Lapin XXVII; contrôle des capsules surrénales).

Cette intoxication étant également proportionnelle à la *quantité* de toxine et à la *surface* frictionnée, il ne faut pas augmenter ni la quantité de mélange qu'on dépose sur la peau; ni la surface de friction, tant que la teneur antitoxique du sérum est insuffisante.

Lorsque le sérum contient plus de 1/2 unité antitoxique par cm³, ces deux facteurs peuvent varier sans inconvénient.

Ces conditions expérimentales étant respectées, le lapin supporte très bien des concentrations qui, employées d'emblée, auraient provoqué sa mort.

Les délais entre les opérations successives sont d'un minimum de 3 semaines mais peuvent, bien entendu, être largement dépassés (Cf Tableaux).

Jusqu'à présent, lorsque nous n'avons plus eu de réponse cutanée avec 28 unités, nous n'avons pas employé la solution d'un titre antigénique plus élevé. Y a-t-il avantage à les utiliser?

Le nombre d'unités antitoxiques du sérum continue-t-il à augmenter proportionnellement au nombre d'unités antigéniques, alors que la peau ne réagit plus que par un érythème. En d'autres termes, *y a-t-il absorption par la peau sans que celle-ci fasse de réaction notable?*

Le contrôle du pouvoir antitoxique du sérum des animaux en expérience a été fait par le Professeur Paul Bordet à l'Institut Pasteur de Bruxelles.

Notons que les animaux dont la réaction cutanée est le plus intense ne sont pas nécessairement ceux qui se vaccinent le plus rapidement.

Nous avons titré les unités antitoxiques du sérum des lapins qui, après avoir été frictionnés 2 ou 3 fois avec 14 unités, n'avaient pas réagi à une friction suivante avec la même concentration.

Dans certains cas, le sérum contenait déjà plus d'une demi unité antitoxique par cm^3 ; dans d'autres, au contraire, il titrait moins de 1/10ème d'unité antitoxique.

Nous avons pu constater que les premiers ne réagissent pas non plus aux mélanges 20 unités et 28 unités, tandis que ceux dont le sérum titre moins de 1/2 unité antitoxique par cm^3 peuvent faire des réactions cutanées nettes avec les mélanges 20 et 28 unités antigéniques (L IV, L V, L XI).

Après ces frictions complémentaires, le sérum titre plus d'une demi unité antitoxique.

En effet, le sérum de *tous* nos lapins qui ont été frictionnés avec 20 et 28 unités dose toujours, *sans exception*, plus d'une demi unité antitoxique, parfois même plus d'une unité.

Dans certains cas nous avons fait plusieurs titrages en cours de vaccination. Nous avons ainsi, chez certains lapins, titré successivement moins de 1/10ème, moins de 1/2 et plus d'une demi unité antitoxique par cm^3 (L VII).

La lecture analytique des tableaux des animaux en expérience nous permet d'affirmer qu'il *n'est pas nécessaire que la peau réagisse violemment pour que le pouvoir antitoxique du sang augmente.*

Partant de cette donnée, nous faisons actuellement des essais de vaccination en modifiant notre méthode. Nous utilisons des concentrations n'amenant comme réaction qu'un érythème.

Désignation	Réaction + le X ^e jour	Intensité de la Réaction	Eschare ou croûte tom- bées le X ^e jour	Unités employées
C II 27—I—47 1×3 cm	1 ^{er}	E. I. croûte noire	13 ^e	26
1—III 2×3 ¹ / ₂ 3 gouttes	1 ^{er}	E. I. croûte noire		28
C IX 3—VI—47 2 ¹ / ₂ ×3 ¹ / ₂ 4 gouttel.	1 ^{er}	E. I. croûtelles grisâtre humide		28
C X 3—VI—47 2 ¹ / ₂ ×3 ¹ / ₂ 4 gouttel.	1 ^{er}	E. I. croûte humide		20 toxine glycér.
C XI 3—VI—47 2 ¹ / ₂ ×3 4 gouttel.	1 ^{er}	E. I. croûte noire		20 toxine 3 glycér. 2 Ephys. 1
C I 26—VIII—46 2 ¹ / ₂ ×3	1 ^{er}	E. I. croûte noire		28 toxine 2 glycér. 1
C III 20—V—47 1×1 cm 1 gouttelette	1 ^{er}	E. I. croûte noire	8 ^e	20
C IV 20—V—47 1×1 cm 1 gouttelette	1 ^{er}	E. I. croûte noire	10 ^e	20
C V 20—V—47 1×1 ¹ / ₂ cm 1 gouttelette	1 ^{er}	E. I. croûte noire	11 ^e	20
C VI 20—V—47 2 ¹ / ₂ ×4 cm 2 gouttel.	1 ^{er}	E. I. légers fine croûtelles	5 ^e	20
C VII 20—V—47 4 ¹ / ₂ ×6 cm 3 gouttel.	1 ^{er}	E. I. légers croûtelles jaune	10 ^e	20

C = Cobaye.

L = Lapin.

E = érythème.

I = infiltration.

Date de la préparation	PH	Unités antitoxiques du sérum	Notes	Poids
10—XII	7 ¹ / ₂			27—I—47 I. 395 g
1—III	7 ¹ / ₂		meurt 5 ^{me} j. surrénales N myocarde mou péritoine rouge	3—II 395 g 1—III 365 g
20—V	7 ¹ / ₂		meurt 3 ^{me} j. surrénales hé- morragiques	280 g
20—V	7 ¹ / ₂		meurt 3 ^{me} j. surrénales hé- morragiques	360 g
2—VI	7 ¹ / ₂		meurt 6 ^{me} j. surrénales hé- morragiques	330 g
26—VIII	7 ¹ / ₂		meurt 5 ^e jour	
27—IV	7 ¹ / ₂		toxine concentrée sur petit espace; grosse réaction locale	20—V—47 380 g 27—V—47 395 g
27—IV	7 ¹ / ₂		toxine concentrée sur petit espace; grosse réaction locale	20—V 440 g 27—V 445 g
27—V	7 ¹ / ₂		idem	20—V 465 g 27—V 460 g
27—V	7 ¹ / ₂		toxine étalée sur+grand espace; moins grosse réaction locale	20—V 415 g 27—V 460 g
27—V	7 ¹ / ₂		id. réaction encore moindre que pour le C VI	20—V 440 g 27—V 430 g

Désignation	Réaction + le X ^e jour	Intensité de la Réaction	Eschare ou croûte tom- bées le X ^e jour	Unités employées
C IIX 20—V—47 5×7 cm 4 gouttel.	1 ^{er}	E. I. légers fine croûte jaune non continue	8 ^e	20
L I 28—VIII—46	C: 3 ^e j. P: 1 ^{re}	C: piqûre de moustique P: très grosse I eschare noire		28 28
L XXVII 21—I—47	1 ^{er}	E; croûte jaune, noirâtre au centre	10 ^e	8—10
1—III 2×3 cm	1 ^{er}	E; I légère; eschare noire	22 ^e	14
29—V 2½×4½ cm	1 ^{er}	E, I moyenne 8×6 cm; croûte noire 3×4 cm		20
L XXIX 27—I—47 1½×4 cm	1 ^{er}	E; forte I (4 à 5 cm pro- fondeur) eschare noire	19 ^e	28
1—III	1 ^{er}	E; I moyenne; eschare noire		28
L XXIX 11—II—47 5×5 cm	1 ^{er}	E; I; eschare noire		28
L II 28—VIII—46	1 ^{er}	E; très forte I; eschare	17 ^e	14
26—IX	1 ^{er}	I moyenne; croûte noire	21 ^e	14
5—XI	1 ^{er}	E. croûte jaune	7 ^e	14
10—XII	1 ^{er}	E léger, squames	4 ^e	14
7—I—47		E léger		14
5—VI	1 ^{er}	E léger, pellicule desquamante	4 ^e	20

C = cutiréaction.

P = percutiréaction.

Date de la préparation	PH	Unités antitoxiques du sérum	Notes	Poids
27—V	7 $\frac{1}{2}$		id. réaction encore moindre que pour les C VI et C VII	20—V 405 g 27—V 420 g
26—VIII	7 $\frac{1}{2}$		meurt 40 h. après réaction	
30—IX	7			27—I—47 2 680 g 3—II 2 950 g 10—II 2 975 g 10—III 2 810 g 8—IV 2 750 g 5—V 3 060 g 27—V 3 100 g 2—VI 2 650 g
I—III	7 $\frac{1}{2}$			
29—V	7 $\frac{1}{2}$		meurt dans la nuit du 2 au 3 capsules surrénales brunes Sous la réaction tissus rouges	
10—XII	7 $\frac{1}{3}$			27—I 2 150 g 3—II 2 155 g 10—II 2 260 g
I—III	7 $\frac{1}{2}$		meurt le 7 ^e j. surrénales grosses mais non hémorragiques voir cobaye II	
10—XII	7 $\frac{1}{2}$		meurt 3 ^{me} jour surrénales hémorragiques Myocarde mou péritoine rouge foie: pîcté hémorragique	2 090 g
26—VIII	7 $\frac{1}{2}$		réaction trop sévère avec 14 u. d'emblée	
26—IX	7 $\frac{1}{2}$			
25—X	8			
10—XII	7 $\frac{1}{3}$			
10—XII	7 $\frac{1}{2}$	15—I—47, plus de $\frac{1}{2}$ par cc		27—I—47 3 420 g 10—II 3 400 g
29—V	7 $\frac{1}{2}$		donc 6 mois après le pouvoir antitoxique du sérum est resté élevé	10—III 3 470 g 8—IV 3 210 g 12—V 3 290 g 2—VI 2 810 g 9—VI 3 040 g

Désignation	Réaction + le X ^e jour	Intensité de la Réaction	Eschare ou croûte tom- bées le X ^e jour	Unités employées
L III				
3—IX—46	1 ^{er}	E; I légère; croûte noire	18°	9—10
26—IX	1 ^{er}	E; I légère; fine croûte	15°	14
10—XII	1 ^{er}	E léger; pellicule	4°	14
7—I—47	1 ^{er}	E		14
L IV				
8—X	1 ^{er}	E et I légers; fine croûte jaune	6°	9—10
13—XI	1 ^{er}	E; croûte desquamante	5°	14
10—XII	1 ^{er}	E; I légère; croûte noire	8°	14
7—I—47	1 ^{er}	E ?		14
28—III	1 ^{er}	E croûte noire	17°	28
29—V 3×4 cm	1 ^{er}	E; I légère; fine pellicule	5°	28
L V				
13—IX—46	1 ^{er}	E, I légers, croûte	8°	9—10
10—XII	1 ^{er}	E; pellicule jaune, tache noire	6°	10
7—I—47	1 ^{er}	E léger; fine pellicule	4°	14
27—I	1 ^{er}	E léger		14
28—III	1 ^{er}	E, I moyenne, croûte noire	19°	28
29—V 2 gouttes 3×4 cm	1 ^{er}	E, I légère, fine pellicule		28
L VII				
19—IX—46	1 ^{er}	E; I légère; croûte grise	14°	9—10
14—XI	1 ^{er}	Négatif		14

Date de la préparation	PH	Unités antitoxiques du sérum	Notes	Poids
3-IX	7			7-IX-46 2 020 g
26-IX	7 ¹ / ₂			4-X 2 100 g
10-XII	7 ¹ / ₂			4-XI 2 550 g
10-XII	7 ¹ / ₂	15-I-47 plus de ¹ / ₂ par cc	meurt par traumatisme le 10-IV-47	2-XII 2 635 g
				6-I-47 2 725 g
				20-I 2 740 g
				3-II 2 635 g
				10-III 2 320 g
8-X	9			7-X-46 2 120 g
13-XI	7 ¹ / ₂			21-X 2 400 g
10-XII	7 ¹ / ₂			5-XI 2 450 g
10-XII	7 ¹ / ₂	15-I-47 entre 1-10 et ¹ / ₂ par cc		25-XI 2 690 g
1-III	7 ¹ / ₂		a réagi violemment à 28 U. parce que le sérum contenait moins de ¹ / ₂ u. par cc	10-XII 3 015 g
				6-I-47 3 125 g
				3-II 3 225 g
				10-III 3 210 g
				31-III 3 160 g
				21-IV 3 200 g
				5-V 3 150 g
				27-V 3 220 g
				9-VI 3 209 g
				16-VI 3 250 g
29-V	7 ¹ / ₂	12-VI-47 plus de ¹ / ₂ par cc		
13-IX	7			19-IX-46 2 150 g
10-XII	7			5-X 2 300 g
10-XII	7 ¹ / ₂			4-XI 2 700 g
10-XII	7 ¹ / ₂	11-II-47 moins de ¹ / ₂ par cc		2-XII 2 810 g
1-III	7 ¹ / ₂		a réagi violemment à 28 U. parce que le sérum contenait moins de ¹ / ₂ u. par cc	6-I-47 3 040 g
				3-II 3 260 g
				10-III 3 215 g
				8-IV 2 930 g
				21-IV 3 130 g
				5-V 3 025 g
				5-VI 2 750 g
29-V	7 ¹ / ₂	12-VI-47 plus de ¹ / ₂ u. par cc		
19-IX	7		contrôle à la toxine chauffée, amène un E (négatif le 3 ^e j.)	19-IX-46 2 450 g
13-XI	7 ¹ / ₂	18-XI-46 moins de ¹ / ₁₀ par cc		10-X-46 2 800 g
				4-XI 3 130 g
				2-XII 3 250 g

Désignation	Réaction + le X ^e jour	Intensité de la Réaction	Eschare ou croûte tom- bées le X ^e jour	Unités employées
16—XII en deux endroits	1 ^{er}	E; I; croûte noire	6 ^e	14
21—I	1 ^{er}	E; fine croûte jaune	15 ^e	14
1—III	1 ^{er}	E; fine pellicule	6 ^e	21
28—III 3 × 4 cm	1 ^{er}	E	6 ^e	21
29—V 2 gouttes 2 × 3 cm	1 ^{er}	E, I légers fine pellicule	9 ^e	2
L XI				
23—XI—46	1 ^{er}	E; croûte jaunâtre	7 ^e	9—10
30—XII	1 ^{er}	E; I légère croûte jaune	9 ^e	14
27—I—47	—	—		14
28—III 3 × 4	1 ^{er}	E, I. croûte noire	25 ^e	28
29—V 2 gouttes thorax 2 1/2 3 1/2	1 ^{er}	E, I. légère 3 × 4 pellicule	8 ^e	28
L XII				
30—IX	1 ^{er}	E; I légère croûte noire	9 ^e	9—10
10—XII	1 ^{er}	E, I; croûte noire	10 ^e	10
7—I—47	1 ^{er}	E, fine croûte jaune	8 ^e	14
27—I	1 ^{er}	E, Squames		14
5—VI	1 ^{er}	E, pellicule	5 ^e	20
L XIII				
7—X—46	1 ^{er}	E, I légère croûte noire	8 ^e	9—10
10—XII	1 ^{er}	E, très fine croûte jaune	9 ^e	10
7—I	1 ^{er}	E, fine croûte noire	17 ^e	14
27—I	1 ^{er}	E, pellicule jaune	7 ^e	14

Date de la préparation	PH	Unités antitoxiques du sérum	Notes	Poids
10—XII	7 $\frac{1}{2}$	t	donc après une réaction négative à 14 u.; réaction marquée avec 14 u.	6—I—47 3 445 g 9—II 3 350 g 10—III 3 410 g 8—IV 3 300 g 2—VI 3 180 g 16—VI 3 340 g
10—XII	7 $\frac{1}{2}$			
1—I—I	7 $\frac{1}{2}$			
1—I—I	7 $\frac{1}{2}$	10—IV—47 moins de $\frac{1}{2}$ u. par cc		
29—V	7 $\frac{1}{2}$	12—VI—47 plus de $\frac{1}{2}$ u. par cc	Malgré réactions minimales de la peau, le pouvoir antitoxique du sérum a augmenté	
13—XI	7 $\frac{1}{2}$			23—XI—46 3 150 g 23—XII 3 300 g 13—I—47 3 390 g 3—II 3 510 g 10—III 3 420 g 31—III 3 030 g 28—IV 3 200 g 27—V 3 190 g 16—VI 3 170 g
10—XII	7 $\frac{1}{2}$			
10—XII	7 $\frac{1}{2}$	le 11—II prélèvement de sang; moins de $\frac{1}{2}$ u. a. par cc		
1—III	7 $\frac{1}{2}$		réaction forte parce que le sérum contenait moins de $\frac{1}{2}$ u. par cc	
29—V	7 $\frac{1}{2}$	le 11—VI: plus de $\frac{1}{2}$ u. par cc		
30—IX	7			30—IX 2 450 g 21—X—46 3 000 g 18—XI 3 130 g 2—XII 3 190 g 7—I—47 3 530 g 3—II 3 710 g 10—III 3 690 g 31—III 3 370 g 28—IV 3 400 g 27—V 3 390 g 16—VI 3 430 g
10—XII	7 $\frac{1}{2}$			
10—XII	7 $\frac{1}{2}$			
10—XII	7 $\frac{1}{2}$	le 11—II: plus de $\frac{1}{2}$ u. par cc		
29—V	7 $\frac{1}{2}$		Donc 5 mois et demi plus tard le pouvoir antitoxique du sérum est resté élevé	
30—IX	7			7—X—46 2 530 g 18—XI 3 100 g 10—XII 3 270 g 7—I—47 3 190 g 3—II 3 185 g 10—III 3 300 g
10—XII	7			
10—XII	7 $\frac{1}{2}$			
10—XII	7 $\frac{1}{2}$			

Désignation	Réaction + le X ^e jour	Intensité de la Réaction	Eschare ou croûte tom- bées le X ^e jour	Unités employées
1—III	1 ^{er}	E, I croûte jaune noire	26°	14
21—V 3 × 3 ¹ / ₂	1 ^{er}	E, I, fine pellicule	3°	20
29—V 2 gouttes 2 ¹ / ₂ 3 ¹ / ₂	1 ^{er}	E, I légère, pellicule	5°	28
L XV 23—X—46	1 ^{er}	E, très fine croûtelte	9°	9—10
18—XI	1 ^{er}	E, I légère; croûtelte noirâtre	15°	10
30—XII	1 ^{er}	E; forte I; croûte noire	13°	14
27—I—47	1 ^{er}	E; croûtelte noire	9°	14
1—III	1 ^{er}	E, I, croûte noire	30°	14
21—V 3 ¹ / ₂ × 3 ¹ / ₂	1 ^{er}	très léger E		14
29—V 1 goutte 2 × 4	1 ^{er}	E, I légère, fine pellicule	5°	20
L XVI 18—XI—46	1 ^{er}	E, I légère; croûtelte	10°	9—10
30—XII	1 ^{er}	E, mince croûtelte	7°	14
21—I—47	1 ^{er}	E, pellicule	7°	14
1—III	1 ^{er}	E, I légère; pellicule	6°	14
28—III 3 × 4	1 ^{er}	E, I légère	6°	28
29—V 3 × 5 2 gouttes	1 ^{er}	E, pas I, fine pellicule		28
L XVII 4—XI—46	1 ^{er}	E, I; eschare noire	20°	9—10
10—XII	1 ^{er}	E, I, légère croûte jaune	11°	10
7—I—47	1 ^{er}	E? fine pellicule desquamante		14
27—I	—	—		14
28—III 3 × 4	1 ^{er}	E, I légers fine pellicule	8°	28
21—V 2 × 3	1 ^{er}	E léger	2°	28
29—V 3 × 4 3 gouttes	1 ^{er}	E I légers pellicule	8°	28

Date de la préparation	PH	Unités antitoxiques du sérum	Notes	Poids
1-III	7 $\frac{1}{2}$	t		8-IV 3 090 g
27-IV	7 $\frac{1}{2}$			5-V 3 130 g
				2-VI 3 070 g
29-V	7 $\frac{1}{2}$	le 11-VI-47 plus de $\frac{1}{2}$ u. par cc		
30-IX	7			18-X-46 2 430 g
13-XI	7 $\frac{1}{2}$			4-XI 2 780 g
10-XII	7 $\frac{1}{2}$			25-XI 2 930 g
10-XII	7 $\frac{1}{2}$			18-XII 3 365 g
1-III	7 $\frac{1}{2}$			20-I-47 2 705 g
1-III	7 $\frac{1}{2}$			3-II 2 700 g
1-III	7 $\frac{1}{2}$			10-III 2 490 g
				8-IV 2 470 g
				5-V 2 810 g
				9-VI 2 830 g
29-V	7 $\frac{1}{2}$	le 11-VI-47 plus de $\frac{1}{2}$ u. par cc		
30-IX	7			18-XI-46 2 960 g
10-XII	7 $\frac{1}{2}$			18-XII 3 405 g
10-XII	7 $\frac{1}{2}$			20-I 2 930 g
1-III	7 $\frac{1}{2}$			3-II 3 470 g
1-III	7 $\frac{1}{2}$	Plus de $\frac{1}{2}$ u. par cc		10-III 3 100 g
				8-IV 3 210 g
				12-V 3 400 g
				16-VI 3 200 g
29-V	7 $\frac{1}{2}$	Plus de 1 u. par cc		
30-IX	7			4-XI-46 2 120 g
10-XII	7			2-XII 2 435 g
10-XII	7 $\frac{1}{2}$			6-I-47 2 755 g
10-XII	7 $\frac{1}{2}$			3-II 3 020 g
10-XII	7 $\frac{1}{2}$	le 11-II-47: moins de $\frac{1}{2}$ u. par cc		10-III 2 960 g
1-III	7 $\frac{1}{2}$			8-IV 2 710 g
1-III	7 $\frac{1}{2}$			5-V 2 985 g
				9-VI 2 980 g
29-V	7 $\frac{1}{2}$	le 12-VI: plus de $\frac{1}{2}$ u. par cc	Malgré aréactivité relative de la peau le pouvoir antitoxique du sang augmente	

Désignation	Réaction + le X ^e jour	Intensité de la Réaction	Eschare ou croûte tom- bées le X ^e jour	Unité employée
L XIII				
29—XI—46	1 ^{er}	E, fine croûte jaune	6 ^e	9—10
30—XII	1 ^{er}	E, pellicule	5 ^e	14
21—I—47	1 ^{er}	E, croûte noire	17 ^e	14
L XIV				
1—III	1 ^{er}	E, I légère; pellicule	6 ^e	14
28—III 3×4 cm	1 ^{er}	E, I légère; pellicule	6 ^e	28
21—V 4×5 cm	1 ^{er}	E, I très légers	4 ^e	28
29—V 2 gouttes 2½×3½ cm	1 ^{er}	E, I très légers fine pellicule desquamante	5 ^e	28
L XX				
27—XI	1 ^{er}	E, léger		9—10
30—XII	1 ^{er}	E? quelques squames		14
21—I—47	1 ^{er}	E, croûte noire	14 ^e	14
L XXI				
1—III	1 ^{er}	E; I moyenne; eschare	31 ^e	28
21—V 3×3	1 ^{er}	E—I très légers, fine pellicule desquamante	6 ^e	28
L XXII				
25—XI	1 ^{er}	E, I moyenne croûte noire	11 ^e	9—10
30—XII	1 ^{er}	E, tache noire croûte jaune	8 ^e	14
21—I—47	1 ^{er}	E, croûte jaune et noire	9 ^e	14
1—III	1 ^{er}	E, I légère; croûte jaune et noire	16 ^e	14
28—III	1 ^{er}	E, quelques squames	6 ^e	14
21—V 3×3	1 ^{er}	E, I légers; quelques squames	5 ^e	20
29—V 2 gouttes 2½×3½	1 ^{er}	E, pas I, fine pellicule	5 ^e	28
L XXIII				
10—XII—46	1 ^{er}	E; I légère croûte jaune	15 ^e	10
7—I—47	1 ^{er}	E; I légère croûte noire	15 ^e	14
27—I	1 ^{er}	E; croûte jaune	10 ^e	14

Date de la préparation	PH	Unités antitoxiques du sérum	Notes	Poids
13—XI	7 ¹ / ₂			7—XI 1 900 g
10—XII	7 ¹ / ₂			11—XII 2 640 g
10—XII	7 ¹ / ₂		réaction beaucoup plus forte que le 30—XII avec même réactif	6—I 2 885 g
				3—II 2 965 g
				10—III 3 030 g
1—III	7 ¹ / ₂			14—IV 3 020 g
1—III	7 ¹ / ₂			12—V 3 210 g
1—III	7 ¹ / ₂			9—VI 3 110 g
20—V	7 ¹ / ₂	le 12—VI plus de ¹ / ₂ u. par cc		
13—XI	7 ¹ / ₂			23—XI—46 2 040 g
10—XII	7 ¹ / ₂			23—XII 2 650 g
10—XII	7 ¹ / ₂		réagit beaucoup plus à même titrage que le 30—XII	20—I—47 2 810 g
				3—II 2 880 g
1—III	7 ¹ / ₂			10—III 2 735 g
1—III	7 ¹ / ₂	le 11—VI plus de ¹ / ₂ u. par cc		8—IV 2 620 g
				9—VI 2 660 g
13—XI	7 ¹ / ₂			25—XI—46 1 880 g
10—XII	7 ¹ / ₂			23—XII 2 585 g
10—XII	7 ¹ / ₂			20—I—47 2 620 g
1—III	7 ¹ / ₂			3—II 2 730 g
				10—III 2 610 g
1—III	7 ¹ / ₂	Plus de ¹ / ₂ u. par cc		8—IV 2 620 g
				5—V 2 670 g
27—IV	7 ¹ / ₂			9—VI 2 630 g
20—V	7 ¹ / ₂	plus de 1 u. par cc		
10—XII	7			19—XII—46 1 930 g
10—XII	7 ¹ / ₂			6—I—47 2 075 g
10—XII	7 ¹ / ₂			3—II 2 080 g
				10—III 2 150 g

Désignation	Réaction + le X ^e jour	Intensité de la Réaction	Eschare ou croûte tom- bées le X ^e jour	Unités employées
1—III superficie	1 ^{er}	E; I légère croûte noire	18 ^e	14
28—III	1 ^{er}	E	4 ^e	14
21—V 3×3	1 ^{er}	E léger	3 ^e	20
29—V 2 gouttes 2 $\frac{1}{2}$ ×3 $\frac{1}{2}$	1 ^{er}	E, pas I pellicule fort détachée	6 ^e	28
L XXIV 16—XII—46	1 ^{er}	E; eschare noire	12 ^e	10
7—I—47	1 ^{er}	E; croûte noire	9 ^e	14
27—I	1 ^{er}	E; fine croûte noire	8 ^e	14
1—III superficie	1 ^{er}	E; I légère; croûte noire	18 ^e	14
28—III	1 ^{er}	E		14
21—V 3×3	1 ^{er}	E très léger		20
29—V 3×4 2 gouttes	1 ^{er}	E, I très légère 2×4 fine pellicule	6 ^e	28

L'intensité de la réaction à la peau dépend de facteurs individuels.

Certains animaux ne réagissent jamais très fort, alors que cependant ils se vaccinent rapidement (L III, VII, XII, XV, XXI).

D'autres, au contraire, ont toujours des réponses cutanées violentes jusqu'au moment où ils sont vaccinés.

Il arrive, par ailleurs, qu'un animal donné réagisse plus à certains moments qu'à d'autres, les conditions expérimentales restant les mêmes (L VII, XX et XXVI).

Ces phénomènes qui existent vraisemblablement chez l'homme comme chez l'animal, doivent intervenir pour expliquer le pourcentage d'erreurs que comporte la recherche des sujets réceptifs à la diphtérie lorsque l'on se base sur une réaction cutanée; mais l'on ne peut exiger que des phénomènes biologiques soient mathématiques comme l'est un phénomène chimique.

Date de la préparation	PH	Unités antitoxiques du sérum	Notes	Poids
1-III	7 $\frac{1}{2}$	(8-IV-47 2 330 g 12-V 2 610 g 9-VI 2 760 g
1-III	7 $\frac{1}{2}$			
27-IV	7 $\frac{1}{2}$		on augmente impunément la surface de friction	
29-V	7 $\frac{1}{2}$	Le 11-VI-47 plus d'une $\frac{1}{2}$ u. par cc	on augmente la quantité de toxine impunément	
10-XII	7			18-XII-46 2 280 g
10-XII	7 $\frac{1}{2}$			13-I-47 2 485 g
10-XII	7 $\frac{1}{2}$			3-II 2 720 g
1-III	7 $\frac{1}{2}$			10-III 2 685 g
				31-III 2 690 g
				21-IV 2 760 g
				19-V 3 050 g
1-III	7 $\frac{1}{2}$		augmentation de la surface de friction	16-VI 2 870 g
27-IV	7 $\frac{1}{2}$			
29-V	7 $\frac{1}{2}$	Le 11-VI-47 plus d'une $\frac{1}{2}$ u. par cc	à huit jours d'intervalle on augmente la surface de friction et la quantité de toxine impunément	

Ces variations que la peau subit, sa façon individuelle de réagir, que nous avons constatées ici dans nos recherches personnelles, sont sans doute vraies pour toutes les réactions cutanées.

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The Relation of the Types of *Corynebacterium Diphtheriae* to Diphtheria.

Presented at section 3 by **Sp. Charocopos** and **J. Margaritis**.

From the Children Clinic of Athens University. Director Prof. G. N. MAKKA.

Between October 1937 and April 1940 we studied 418 Strains of *Corynebacterium diphtheriae* isolated from patients of the Children's Clinic and 42 strains from healthy carriers.

Specimens of the throat or nose secretions were obtained on sterile swabs and planted on Löffler's medium. At the same time direct planting on Clauberg's II, Clauberg's III or Tietz's media was made. The cultures were examined after 24 hours. If they were suspicious or positive, smear preparations were stained by Gram, Neisser—Gins, and Stoltenberg Staining methods. When the clinical diagnosis was confirmed the incubation of cultures was interrupted; otherwise it was continued for another 24 hours. Every primary culture on Löffler's medium was inoculated on meat infusion broth and starch-peptone-serum and incubated for 5 days.

The stability of the types was studied only on 30 strains, ten of each type, by inoculating every month from positive colonies on Löffler's serum where the strains were kept in culture media of macroscopical and biochemical differentiation (s. a.). War conditions interrupted this part of the work after six months.

The virulence test of the isolated strains was done on 3 gravis, 11 intermedius and 20 mitis strains by the hypodermic injection of 0.2 cc of a suspension of 500 000 000 bacilli per cc in 0.9 % (NaCl) Sodium Chloride in guinea pigs, which were later examined by autopsy.

The results of our research are shown in the table. From this table we determined the mean (N. p.), the standard deviation ($\sigma = \sqrt{N \cdot p \cdot q}$), the statistical significance of the difference in pairs $\left(\frac{\text{diff.}}{\sigma \text{ diff.}} > 3 \right)$ and the correlation factor $r_{ab} = \left[\frac{\sum XY}{N} - (v_a \cdot v_b) \right] \cdot \left(\frac{1}{\sigma'_a \times \sigma'_b} \right)$ between type and clinical picture.

TABLE 1. Types of corynebacterium diphtheriae after origin, sex, age, months, location, clinical picture, complications and fatality.

		Corynebacterium diphtheriae			Total
		Type gravis	Type mitis	Type inter- medium	
Origin of strains	Patients	7	144	267	418
	Healthy carriers	3	18	21	42
Sex	Males	5	102	111	218
	Females	2	42	156	200
Age	0-5	7	106	216	329
	6+	0	38	51	89
Months	January	1	19	35	55
	February	—	11	31	42
	March	2	1	15	18
	April	—	4	9	13
	May	—	4	8	12
	June	—	2	4	6
	July	—	2	3	5
	August	—	4	7	11
	September	—	9	14	23
	October	2	30	44	76
	November	1	33	49	83
	December	1	25	48	74
Location	Pharynx	2	106	164	272
	Larynx	3	9	33	45
	Pharynx & Larynx	2	21	54	77
	Nose	0	8	16	24
Clinical picture	Light	1	85	143	229
	Moderate	2	27	33	62
	Severe	4	32	91	127
Complications	Myocarditis	4	8	21	33
	Polyneuritis	1	0	2	3
	Stenosis catheterised	2	26	41	69
	Tracheotomy	—	5	26	31
Fatality		4	11	23	38

In accordance with the results of those determinations the general results of our experience are as follows:

1. Except for type gravis, whose cases are few, *t. intermedius* is dominant.
2. Diphtheria is a disease of the first infancy (age 0—5 years 79 %; age 6 and above years, 21 %) in epidemics and in the ensuing latent immunization.
3. Types mitis and intermedius show a temporary increase, as does clinical diphtheria during the months of September, December, and January, and March.
4. Correlation between type and clinical picture does not exist ($\tau_{ab} = 0.0651 \pm 0.0152$).
5. Preference in regard to localization or complications of a fixed type was not observed.
6. The cause of the high fatality (9 %) is the occurrence of the disease in children under five years of age, and delay in the administration of anti-toxin.

The Treatment (Prophylaxis) of Acute Anterior Poliomyelitis.

By Prof. Dr. **Jar. Procházka**, Prague, Czechoslovakia.

According to our experience the treatment of A. P. M. is only possible during the stage of meningeal irritation.

All of our 1486 cases of A. P. M. in children showed signs of meningeal irritation. Each case started with the picture of meningitis serosa.

Treatment with convalescent anti-serum taken 1—2 year after the onset of the disease was without effect. This treatment has now been generally abandoned.

In the year 1939 we had an insufficient quantity of convalescent serum. We therefore used the blood from convalescent cases still in hospital, and found that if given in sufficient doses, during the stage of meningeal irritation it was able to prevent the development of paralysis.

During the big epidemic in 1939 patients who were not treated, or who were treated by convalescent anti-serum as usually prepared, developed paralyzes in 15—19 % of the cases. Control experiments were not made during the epidemic but proof was gained from the cases treated in our or other departments as suffering from encephalitis, cerebro-spinal meningitis, typhoid fever, or intoxication which in due course revealed themselves as cases of typical A. P. M. Paralysis occurred in patients who did not receive convalescent blood or plasma, and in the cases apart from or at the commencement of an epidemic when convalescent blood was not available.

Convalescent blood or plasma must be taken 7—14 days after the fall of the temperature to normal, at which time it contains in our opinion, the greatest quantity of anti-bodies. Similarly in measles it has been proved that the convalescent blood is most potent 7—9 days after the fall in temperature.

From 1939 to the present time we have treated 1486 cases of A. P. M. 784 of these were admitted during the meningeal stage. The other were brought to the hospital only after the paralysis had already appeared.

Of the patients who received blood from early convalescent cases, only 4 developed paralysis in one case only 20 ccs of convalescent serum was given, and paralysis appeared in 12 hours. In the second the onset of the paralysis was only 6 hours after the injection, signifying that the injection, was given too late.

The criticism that the use of convalescent serum has previously been found to be ineffective may be answered by the fact that the blood was taken too late during convalescence.

During an epidemic of A. P. M. which occurs regularly from July to November every patient with the meningitis serosa confirmed by lumbar puncture is immediately given a transfusion of convalescent blood. It is unavoidable that cases of TB meningitis and cerebro-spinal meningitis are included. But this does not matter. Gut side an epidemic period, when other diseases ea. mumps, Weils disease or encephalomyelitis are relatively more frequent, the cases are investigated before treatment is given.

Summary.

Convalescent blood or plasma given during the meningeal stage prevents the development of paralysis. The transfusion must be made immediately and 60—80—100—120 ccm of blood given according to the age of the patient.

Blood must be taken from a patient 7—14 days after the fall of the temperature to normal. The greatest concentration of antibodies are found at this time.

Blood taken later in convalescence i.e. after 3 who, has only the same effect as adult blood and is of no prophylactic value.

After the appearance of paralysis treatment with convalescent blood is without effect on the course of the others.

Autopyotherapy of Acute Hematogenous Osteomyelitis.

By **A. Makkai** and **Ch. Waltner**, Budapest, Hungary.

(Summary.)

Some 80 cases of acute hematogenous osteomyelitis were treated by autopyotherapy — a therapeutic principle introduced by Makai 25 years ago. Pus was aspirated by a thick needle and syringe from the focus of inflammation, determined by the place of the punctum maximum of the pain. 1 cc of unaltered pus was immediately injected in the subcutaneous tissue of the thigh. This procedure was repeated every 5th day (4—8 times), until the production of pus ceased. Sometimes the development of secondary abscesses was observed (in about 5 %). Nevertheless, these abscesses were never found to be dangerous or even serious, and they healed by resorption or spontaneous perforation without requiring surgical drainage. No other treatment was used except immobilization and the application of fomentations. Every case so treated healed without surgical intervention.

Two main principles of autopyotherapy are to be emphasized:

1. Acute suppurations can heal regularly without surgical opening of the focus.
2. Subcutaneous injection of «native», unmodified pus, containing without doubt highly virulent bacteria, does not cause a dangerous progressive septic process, much less a fatal septic condition.

Section 4—Vitamin Requirements and Avitaminoses.

Troubles de croissance chez l'enfant par doses massives de vitamine D₂.

Par MM. S. Briskas et R. Maret, Paris.

(Travail de l'Hôpital des Enfants Malades. Consultation du Professeur agrégé S. BRISKAS.)

La découverte de la vitamine D₂ et son utilisation en pédiatrie est une des plus importantes étapes de la thérapeutique. Mais l'abus de celle-ci détermine certains accidents assez graves, et même mortels, sur lesquels nombre d'auteurs ont récemment insisté. Cependant, il ne nous semble pas que des troubles de la croissance par hypervitaminose D₂ aient été signalés jusqu'à présent.

Nous présentons 3 observations de ces troubles, concernant des enfants ayant reçu des doses très importantes de calciférol.

1^{er} Cas. — Hubert J..., né le 23.11.1936, âgé de 10 ans, pesant 17 K et mesurant 104 cm nous est amené le 30.9.1946 pour insuffisance et pondérale existant depuis 2 ans.

L'enfant a fait, durant le dernier hiver, des épisodes de rhino-pharyngite accompagnés de fièvre oscillant autour de 38° pendant une semaine. Depuis, il a un appétit capricieux, ses nuits sont agitées.

Antécédants familiaux: père et mère sont bien portants, de taille normale tous les deux.

Dans les antécédants personnels, nous notons: naissance à terme avec un poids de 3.500 K, élevé au sein pendant 1 an, oreillons, varicelle et coqueluche entre 4 et 6 ans, angines répétées depuis plusieurs années; il y a 3 ans, à l'âge de 7 ans, néphrite hématurique guérie sans séquelles.

Depuis son plus jeune âge, au moindre incident et tout particulièrement depuis les angines à répétition et la néphrite, l'enfant reçoit par la mère, et sans conseil médical, de la vitamine D₂ (ampoules buvables à

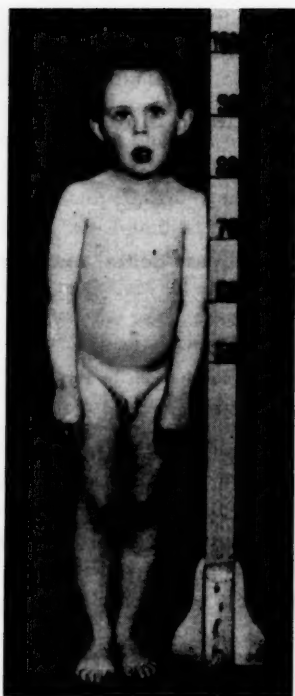


Fig. 1.

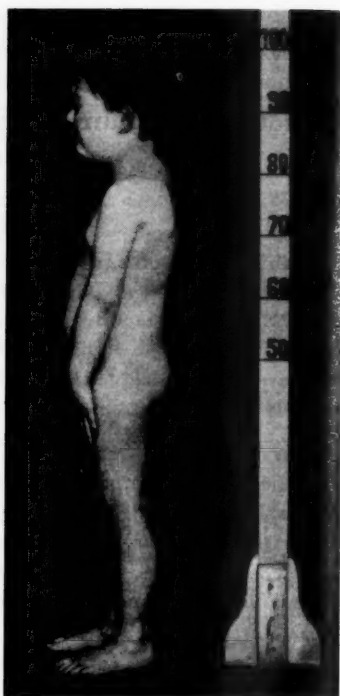


Fig. 2.

Hubert J., né le 23.11. 1936. Agé de 10 ans, poids 17 K, taille 104, reçu 20 000 000 U. I. de vitamine D₂.

15 mmgr. A chaque fois, elle lui administre 2 ampoules à 15 jours d'intervalle et une ampoule tous les mois suivants, au total: 40 ampoules (soit 20 millions d'unités échelonnées sur plusieurs années).

A l'examen, on est en présence d'un enfant pâle, maigre, qui donne l'impression de 4, 5 ans plutôt que de 10 ans. Son visage est cependant normal, la peau est lisse et non ichthiosique, le cholestérol sanguin est normal. Cependant, il existe une hypotonie musculaire très accusée. (Voir Fig. 1 et 2.)

L'examen du système nerveux ne montre rien de particulier. Au point de vue digestif, rien à signaler. Le foie déborde légèrement les faisses côtes, la rate est normale.

L'appareil cardio-vasculaire est normal, la tension artérielle est un peu abaissée à 8,5/5,5.

A l'auscultation des poumons, on constate quelques râles se modifiant après la toux. La Radiographie pulmonaire est normale. Les amygdales sont grosses et s'accompagnent d'une adénopathie cervicale bilatérale.

Les testicules sont normaux.

L'examen clinique du squelette ne révèle rien d'anormal, tant au crâne qu'aux épiphyses et aux os longs. A la Radiographie, on constate:

- au niveau du poignet, absence du point d'ossification de la styloïde cubitale, présence de 7 points d'ossification carpiens, mais non évolués, ce qui correspond environ à un âge de 5 ans 1/2,
- au niveau du crâne, pas d'anomalies, selle turcique normale.

Examens humoraux.

Sédimentation et haptoglobine sont normales.

Calcémie 102 mmg.

Phosphorémie 36 mmg.

Phosphatase 3.2 unités Bodansky.

Urée: 0.25.

Protides 75 g. — Globuline 25, Sérine 50.

Cholestérolémie 1.35.

Urines culot de centrifugation normal

ni albumine, ni sucre.

chlorures: 16 g au litre.

La constante d'Ambard est physiologique.

Numération et formule: Hémoglobine 90,

Globules rouges: 4 500 000

blancs: 11 200

Valeur globulaire: 1

Poly. Neutro: 49, Poly. éosino: 2, Poly. baso: 1. Lymphocytes: 42,

Monocytes: 6.

Ajoutons que les tests de Von Pirquet, de Mantoux, le B. W. Khahn et Mainke sont négatifs.

2^{ème} Cas. — Annie J... née le 21.10.1945, âgée de 8 mois 1/2, pesant 6.900 K, mesurant 57 cm, est amenée à notre consultation le 16.7.1946 pour des tics nerveux.

Antécédants familiaux: rien à signaler.

Antécédants personnels: née à terme, poids de naissance: 3 kg; allaitement mixte, jusqu'à 7 mois, depuis: régime à 5 repas avec bouillie et bouillon de légumes paraissant bien équilibré, première dent à mois 1/2. A l'examen, elle est pâle, très hypotonique et anorexique.

L'examen de radiographie pulmonaire est normal. Le foie déborde légèrement les fausses côtes. La rate et le système nerveux sont normaux.

A l'examen clinique du squelette: le crâne est normal, pas de craniotabès, mais la fontanelle est totalement fermée. L'enfant présente surtout une dentition précoce: 12 dents au premier examen, 16 un mois après par l'apparition de 4 canines.



Fig. 3. Annie J., née le 21.10.1945, âgée de 8 mois 1/2. Montre au carpe, une légère avance d'ossification.

Les radiographies du squelette montrent:

au carpe, une légère avance d'ossification (Fig. 3),
 au crâne, selle turcique normale, voûte crânienne entièrement calcifiée,
 il ne reste qu'une fontanelle de 2 millimètres environ,
 au fémur, point condylien (normal),
 au tibia, points épiphysaires supérieur et inférieur (normal),
 au péroné, point épiphysaire inférieur (soit image de 1 an 1/2),
 au tarse, points cuboïdien et du 1^{er} cunéiforme (soit image de 1 an),
 au rachis, aspect normal.

Nous apprenons par la mère, que, depuis l'âge de 6 mois, sans conseil médical, l'enfant reçoit 2 ampoules de Vitamine D₂ à 15 mmg par mois, soit 8 ampoules absorbées jusqu'à ce jour (4 millions d'unités au total).

Les examens humoraux montrent:

Calcémie: 115 mmg.

Phosphorémie: 40 mmg.

Glycémie: 0.86.

Phosphatase: 5 unités Bodansky.

Protides totaux: 85 g.

Cholestérol: 1.85.

Urée sanguine: 0.25.

Urines: ni sucre, ni albumine.

culot de centrifugation normal.

Constante d'Ambard normale.

Devant ces incidents, on institue un régime et une thérapeutique apportant des quantités importantes de Vitamine A.

Revue depuis, nous notons:

en novembre 1946 — poids 7.750 K (enfant très hypotonique);

à 14 mois (le 27.12.1946) taille 0.78 cm;

à 16 mois (le 10.2.1947) taille 0.80 cm, poids 8.300 K, ne marche pas encore;

à 17 mois (le 15.3.1947) poids 8.800 K;

à 19 mois 1/2 (le 5.6.1947) l'enfant commence seulement à marcher.

3^{ème} Cas. — Françoise R... née le 20 août 1936, âgée de 10 ans 1/2, pesant 23.600 K, mesurant 1.36 m, nous est amenée le 21 janvier 1947 pour maigreur, retard intellectuel et déformation thoracique.

Antécédents familiaux et collatéraux, rien à signaler, sauf, du côté paternel, un gibbeux et un sujet présentant la même déformation que l'enfant.

Antécédents personnels: Née à terme, poids de naissance 4 Kg. Nourrie au sein pendant 1 an. Broncho pneumonie à l'âge de 6 mois. 1^{ère} dentition d'éruption normale. Parle et marche à 15 mois. Rougeole et varicelle entre 7 et 8 ans.

Il y a 3 ans, à l'âge de 7 ans, commence à mal se tenir et se voûte. Bientôt apparaît la déformation thoracique. L'enfant est traitée aussitôt par rayons ultra-violets, calcithérapie, gymnastique corrective. De plus, elle reçoit des ampoules dosées à 15 mmg de vitamine D₂, en 2 séries de 10 ampoules, soit 20 ampoules au total, à raison d'une tous les 2 jours avec repos intercalaire de 1 mois, soit 10 millions d'unités.

A la suite de ce traitement, l'enfant est d'abord plus vivante, mais apparaissent bientôt maigreur et déficience scolaire. De toute façon, aucune action sur la déformation thoracique et l'attitude vicieuse.

A l'examen, on est en présence d'une enfant anorexique amaigrie, malingre et chétive, au dos vouté. La malformation thoracique est importante, asymétrie et proéminence de l'hémithorax droit, proéminence du sternum, déformation du type thorax en carène. (Voir Fig. 4 et 5.)

Son poids est de 23.600 K, sa taille de 1.36 m.

Il existe une hypotonie musculaire importante. Les épreuves dynamométriques montrent:

à droite	17—15—18
à gauche	16—19—20



Fig. 4.



Fig. 5.

Françoise R., née le 20.8.1936, reçue 10 000 000 U. I. de vitamine D₂.

Les appareils: cardio-vasculaire, pulmonaire (radio-pulmonaire normale) digestif sont absolument normaux ainsi que le système nerveux.

Au point de vue intellectuel, il n'y a que défaut d'attention, fatigabilité rapide et manque de mémoire. Néanmoins les réponses aux différents tests d'intelligence sont satisfaisantes.

La cuti et les IDR sont négatives.

L'examen clinique du squelette le montre normal.

Des radiographies du système osseux sont pratiquées:

au crâne: selle turque normale, voûte normale.

aux poignets: 7 points d'ossification normalement évolués pour 10 ans 1/2;

au coude: points épiphysaires du radius et du cubitus, points condylien et épitrochléen sont présents; les points trochléen et épicondylien

manquent encore. Bref aspect normal pour 10 ans 1/2;
au rachis: aspect normal.

Examens humoraux:

Cholestérol: 1.87.

Glycémie: 0.98. †

Protides: 76 g.

Phosphatase: 6 unités Bodansky.

Phosphorémie: 36 mmg.

Calcémie normale: 0.96 mmg.

Urée sanguine: 0.30 p. 1 000.

Urines: absence d'albumine et de sucre. Culot normal.

Constante d'Ambard normale.

Un traitement par vitamine A est institué.

Ultérieurement on note:

le 5.2.1947	poids: 23.900 K
le 12.2.1947	poids: 24 K
le 19.2.1947	poids: 23.700 K

Les trois observations que nous venons de détailler s'opposent les unes aux autres sur de nombreux points.

La première est celle d'un enfant de 10 ans chez lequel les différentes mesures pondérales et staturales correspondent à l'âge de 5—6 ans (1). Aucune cause endocrinienne, ou alimentaire, ne semble pouvoir expliquer ce retard considérable. La néphrite hématurique elle-même n'a été qu'un épisode sans lendemain, et l'hypothèse d'une lésion rénale à l'origine de ce retard ne semble pas pouvoir être retenue. Par contre, l'évolution des troubles pondéraux et staturaux semble bien parallèle à l'administration de Vitamine D₂, à dose totale considérable, mais fractionnée et étagée sur de nombreuses années.

En effet, la croissance, médiocre jusqu'à 7 ans, est totalement arrêtée depuis cet âge, époque à laquelle l'administration de Vitamine D₂ a été intensifiée.

De toute façon, les troubles constatés se résument à:

hypotrophie staturale (104 cm au lieu de 131 cm);
hypotrophie pondérale (17.100 K au lieu de 25.150 K);
hypotonie musculaire;
retard considérable d'ossification.

La deuxième observation est celle d'un nourrisson de 8 mois 1/2 ayant absorbé en 2 mois de la vitamine D à dose totale moins importante mais continue. Sa croissance, normale jusqu'à 6 mois, présente très rapidement des troubles considérables. Aucune cause viscérale ou alimentaire ne peut être invoquée à l'origine de ces troubles, dont l'installation correspond, par contre, à l'administration de vitamine D.

Les troubles constatés sont:

retard pondéral considérable (6.900 K au lieu de 8 à 8.300 à 8 1/2 m);

avance staturale importante (80 cm à 16 mois, ce qui correspond à l'âge de 2 ans);

dentition de lait d'apparition extrêmement précoce (16 dents à 8 mois, ce qui correspond à peu près à 20 mois);

calcification très précoce du crâne (fontanelle fermée à 8 mois), calcification très légèrement en avance au carpe et au péroné;

hypotonie musculaire très accusée;

légère hypercalcémie.

Néanmoins, retard important de la marche, rétabli difficilement à l'âge de 20 mois.

Quant à la 3^{ème} observation, elle concerne une fillette de 10 ans 1/2 qui, 3 ans auparavant, lors de l'apparition d'une déformation squelettique, a absorbé de la vitamine D₂ à dose totale très importante, et de façon massive, sur une période de 3 mois. Depuis cette date, l'enfant présente des troubles que rien ne peut expliquer, en dehors de l'absorption de Vitamine D₂. Ces troubles sont:

un retard pondéral important (23.600 K au lieu de 28 à 29 K);

une hypotonie musculaire très intense;

de légers troubles intellectuels;

par contre, il n'existe ni troubles du développement statural, ni troubles d'ossification.

Ainsi, ces observations comportent, toutes trois, retard pondéral et hypotonie musculaire. Par contre, l'une associe retard statural et retard d'ossification; dans l'autre, coexistent avance d'ossification et de dentition et avance staturale, malgré retard de la marche; dans la dernière, le seul trouble porte sur la croissance pondérale.

Les troubles que nous avons constatés chez nos 3 malades ne correspondent pas sur certains points avec ceux qui ont été signalés jusqu'ici sous le terme de «Hypervitaminose D».

L'action toxique de la vitamine D, administrée à forte dose, a été mise en lumière par de nombreux travaux parus depuis peu tant en Europe (2) qu'aux Etats-Unis (3).

Parmi tous les symptômes cliniques qui ont été décrits, nous retrouvons, dans nos observations, l'hypotonie, l'anorexie, l'amaigrissement, la pâleur, l'asthénie et la lassitude psychique. Par contre, nous n'avons pas retrouvé toute une série de symptômes signalés comme fréquents par nombre d'auteurs (mais non pas comme constants). Aucun de nos cas ne présentait, en effet, de nausées, de constipation, de torpeur, de polyurie, de deshydratation et de soif. Aucun de nos deux grands enfants n'accusait de céphalées, de d'algies. Nous n'avons noté ni tachycardie, ni vertiges, ni épitaxis. Enfin, nous n'avons pas retrouvé les signes neurologiques signalés dans certaines publications.

Les *radiographies du squelette* entier, que nous avons pratiquées, ne nous ont pas montré la présence de calcifications métastasiques (4, 5).

Le *syndrome rénal* (6) signalé par nombre d'auteurs, manquait totalement dans nos cas. Certes, l'un de nos enfants a présenté une néphrite aigüe hématurique 3 ans avant notre examen, mais il ne semble pas qu'elle soit en rapport avec l'administration de vitamine D₂; en effet, elle est survenue à la suite d'une angine, n'a laissé aucune séquelle, et n'a pas été aggravée par l'administration ultérieure de vitamine D₂. De toute façon, l'albuminurie considérée d'ailleurs comme inconstante, n'existait pas chez nos malades. Il n'y avait dans le culot de centrifugation ni leucocytes ni cylindres, ni hématies. La tension artérielle était normale sinon un peu abaissée chez un de nos malades. Le taux d'urée sanguine était normal, ainsi que les diverses épreuves fonctionnelles habituelles (constante d'Ambard, phénolphtaléine etc. . .).

Le *syndrome humoral*, étudié dans les autres publications, diffère en certains points de ce que nous avons constaté dans nos cas.

Certes, la phosphorémie est légèrement augmentée (7), ce qui

semble correspondre aux constatations faites jusqu'ici. Le taux de phosphatase nous est apparu normal.

Les chiffres des protides totaux, sérine et globuline que nous avons trouvés, semblent devoir être considérés comme normaux. En fait, la différence essentielle (7) réside dans le taux de la calcémie. Selon les auteurs, dans presque tous les cas, mais non constamment, existe une hypercalcémie. Or, une seule de nos observations (N° 2) présente une élévation légère de la calcémie à 115 mmg. Dans les 2 autres cas, celle-ci reste normale.

Quant aux *troubles de croissance* si importants que nous avons notés chez nos malades, et qui semblent pouvoir être rapportés à l'administration de Vitamine D₂, aucune observation parvenue jusqu'ici à notre connaissance et concernant des enfants ou des nourrissons ne paraît en faire mention. Certes, expérimentalement et cliniquement, on a noté (8) que l'administration massive de vitamine D₂ peut entraîner une décalcification osseuse plus ou moins importante, portant surtout sur les métaphyses. L'amaigrissement, de même, est signalé dans la majorité des observations, mais c'est un amaigrissement rapide et vite réparable, alors que dans nos cas il s'agit de *retard de croissance pondérale important*. De toute façon, les troubles de la croissance staturale, de la dentition et de l'ossification ne nous semblent pas avoir été jusqu'ici étudiés.

Comment peut-on expliquer le mécanisme de ces troubles?

1°) Dans l'observation 2, la *précocité d'apparition de la première dentition* est un fait remarquable puisque celle-ci était presque complète aux environs de 12 mois. Expérimentalement, l'action de la vitamine D₂ sur la dentition est bien connue. Certains (9) ont estimé que les dents étaient plus sensibles et répondaient plus vite à la vitamine D que les épiphyses. D'autres travaux ont également montré (10) que, chez les jeunes rats, l'administration ou la simple application locale de vitamine D provoquait une éruption dentaire précoce. Notre observation nous semble être, sur le plan clinique, l'illustration de ces travaux expérimentaux.

2°) Le *retard considérable d'ossification* est la caractéristique de l'observation 1. On sait depuis longtemps que la vitamine D possède le pouvoir de mobiliser le calcium fixé sur le squelette.

Certains travaux en ont apporté la preuve (11), en montrant qu'au cours de l'hypoparathyroïdie, la vitamine D, à dose importante, augmentait la calcémie et abaissait la phosphorémie. Il paraît logique d'admettre que, dans notre observation, l'administration de vitamine D à dose considérable (20 millions d'unités) est la cause directe du retard observé, ayant empêché la fixation du calcium sur les points épiphysaires, et l'avant mobilisé là où il était déjà fixé.

3°) *Le phénomène inverse, avance à l'ossification*, résume l'essentiel de notre 2^{ème} observation. Or, certains auteurs, utilisant des isotopes radioactifs du phosphore, ont récemment montré (12), que des quantités modérées de vitamine D augmentaient le pouvoir fixateur de la substance osseuse fondamentale vis à vis du calcium. Faut-il admettre cette explication chez notre malade, qui, ayant absorbé des doses de vitamine D relativement plus faibles que dans le cas N° 1, avait une calcification précoce du crâne, une dentition anormalement avancée, et une légère avance d'apparition de certains points épiphysaires?

4°) *Les troubles du développement statural* ne sont peut-être que le corollaire des troubles de l'ossification. C'est ainsi que chez l'un de nos malades, il y a correspondance entre retard statural et retard d'ossification; à l'inverse, ossification précoce va de pair avec excès de taille. Néanmoins les facteurs de croissance sont multiples; leur mécanisme d'action est encore mal élucidé. Et la question peut se poser, à ce propos, de savoir comment agit la vitamine D. Se borne-t-elle à modifier, dans un sens ou dans l'autre, le métabolisme phospho-calcique? N'agit-elle pas, au contraire, directement sur les facteurs de croissance, tantôt les activant, tantôt les inhibant?

5°) *L'hypotonie musculaire* se retrouve dans les observations que nous rapportons. Son intensité semble suffire à expliquer le retard de la marche observé dans l'observation 2. Mais le rôle de la vitamine D dans son déterminisme apparaît assez obscur. Une telle hypotonie n'est peut-être que la conséquence du trouble du métabolisme calcique, dont on sait le rôle tant au niveau des articulations et ligaments qu'au niveau du système neuro-musculaire.

6°) *Quant à l'insuffisance pondérale*, une interprétation simple

en fait la conséquence de l'anorexie et des troubles digestifs. Certains expliquent (13) ces troubles digestifs par une action directe de l'hypercalcémie sur le tractus digestif. Diverses objections ont déjà été faites à cette hypothèse (14), concernant l'inconstance des lésions anatomiques du tube digestif. Dans nos 3 cas, le taux pratiquement normal de calcémie peut être considéré comme une objection de plus. Faut-il alors, comme précédemment, accorder à la vitamine D, une action directe sur le facteur de croissance pondérale? C'est ce que des travaux expérimentaux que nous avons récemment entrepris sur le rat, permettront peut-être d'élucider.

Enfin, il semble bien qu'à côté de l'action vitaminique elle-même, d'autres facteurs (15) doivent être pris en considération dans le déterminisme des troubles dits d'hypervitaminose D. En effet, l'action vitaminique, à elle seule, ne semble pas pouvoir rendre compte des différences considérables qui existent d'une part entre chacune de nos 3 observations, et d'autre part, entre ces 3 cas et ceux qui ont été jusqu'ici rapportés dans la littérature.

Le mode d'administration est certainement un facteur important. A doses massives et rapprochées, la menace semble aux accidents toxiques et rénaux. A doses plus étagées et prolongées, comme dans nos cas, les troubles de croissance dominent au contraire la scène.

On a, à juste titre, insisté également sur le rôle joué par le capital calcique tissulaire et la ration phospho-calcique, la tolérance étant plus grande à la vitamine D, là où existe une hypocalcémie tissulaire.

De même, certains ont mis en lumière la synergie des vitamines A et D, «la première contrôlant les activités des ostéoblastes, la seconde, le dépôt des sels minéraux».

De plus, le terrain nous semble jouer un rôle essentiel. Une tare rénale n'a peut-être fait qu'aggraver le trouble de croissance dans notre première observation. L'âge des sujets est, de même, un facteur important et toutes les observations concordent à montrer que les troubles d'hypervitaminose D sont d'apparition plus facile et plus précoce chez les jeunes enfants et nourrissons.

Enfin, seul un facteur individuel semble pouvoir expliquer d'une part, les différences de susceptibilité d'un sujet à l'autre, d'autre part, la variabilité des troubles d'hypervitaminose D, tel enfant répondant par des phénomènes toxiques, tel autre par des troubles de croissance.

En conclusion, nous présentons 3 enfants chez qui l'administration de doses très importantes de vitamine D₂ a déterminé l'apparition de troubles de croissance, variables d'un sujet à l'autre. De tels troubles ne nous semblent pas avoir été jusqu'ici signalés chez l'enfant. Par contre, la plupart des signes actuellement décrits, au cours de l'intoxication par vitamine D, manquent dans nos observations. Dans le déterminisme de ces troubles de croissance, l'action de la vitamine D sur le métabolisme phosphocalcique semble jouer le rôle essentiel; mais d'autres facteurs, entre autres (mode d'administration, âge, et susceptibilité individuelle) doivent être invoqués pour expliquer les variations et les contradictions apparentes des divers aspects de l'hypervitaminose D.

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The Subacute Subnutritional Syndrome in Infants.

By **Mamdooh Hanafy**, Alexandria, Egypt.

Introduction.

In this paper the clinical effect of general undernutrition in infants is reviewed. It will be shown that although several clinical pictures may result from malnutrition, they are all consequential stages in the development of one syndrome. The term subacute subnutritional syndrome is proposed for the whole picture.

Trowell¹, Gillman² and other applied the term infantile pellagra to one stage of this syndrome on the evidence of the skin condition, gastrointestinal and nervous symptoms and when they did not respond to nicotonic acid, Trowell applied the term malignant malnutrition. 197 cases collected between 1944—1946 have been studied. They constitute only the severer forms. As 90 % of the cases reported are of the age group 1—3 years, 50 normal controls of the same age group were studied and their average figures were taken as standard. These figures are well known. Two important points are *1st* that the plantar reflex is always flexor and *2nd* that in males the testicles are completely descended to the base of the scrotum.

Stages in the clinical picture.

Age 1—3 years; due to poverty, ignorance or maladvise child received for a few months a high carbohydrate diet consisting only of rice or cereal water and the like.

¹ Trowell, H. C. *Infantile Pellagra*, Tr, ROY, *Soc. Trop. Med. and Hygiene* 33 389, 1940.

² Gillman, T., Gillman, J., Inglis, J., Friedlander, L., and Hammar, E. The substitution of whole stomach extract for Vitamin in the treatment of malignant Infantile Pellagra, *Nature*, London 154: 210 (August 12) 1944.

If we follow a child on such a diet for a long time we find that at first it gains weight although it becomes flabby and may show signs of rickets. Then the weight is maintained at some new level for a short time before it begins to decline. The child is pale, fretful but otherwise normal. Later the clinical picture gradually goes downhill parallel with the loss in weight.

So when the weight loss is mild or grade I ie. within 15 %, the subcutaneous fat is diminished and the child shows cheilosis and signs of riboflavin deficiency. When the weight loss is moderate ie. within 30 % (or grade II), the child has a weak characteristic cry, it is irritable; reflexes diminished; skin dry and inelastic. Edema may appear. As the weight loss increases to within 50 %, severe wasting or grade III we may get one of three clinical pictures.

- a. Wasting, whole syndrome, without skin lesion.
- b. Wasting with pellagrous manifestations.
- c. Wasting with the preascitic stage of liver cirrhosis (a large tender liver with marked tympanitis) with or without pellagrous manifestations.

When the weight loss is over 50 % or grade IV we get either

- a. Marasmus.
- b. Marasmus — pellagrous manifestations.
- c. Marasmus with cirrhosis of liver with or without pellagrous manifestations.

Among our cases of grade III and IV 2 cases presented a picture closely resembling pink disease and 3 resembling Von Jaechth's syndrome.

The Clinical Picture of Subacute subnutritional Syndrome Grade III, Pellagrous.

It usually develops gradually within 2—3 months or follows a long attack of diarrhoea; some of the cases followed measles. The patient is extremely weak, with a pathognomonic long peevish cry; loss of weight above 30 % of the standard. The skin is dry, inelastic, rough and scaly with pigmentations. The lesion starts with bronzed spots, plaques, desquamation and later ulceration.

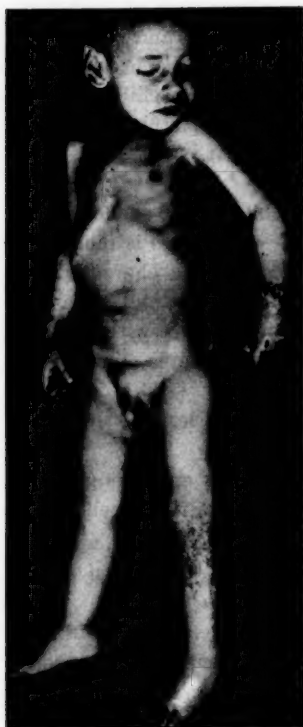


Fig. 1.



Fig. 2.

It involves the buttocks, genitals, legs and feet, shoulders, hands and face. The severity of the disease and its prognosis do not depend on the degree or extent of the skin lesions. Petichoe and ecchymosis may be present, tourniquet test is negative. When edema is present its extent is variable from mere affection of feet and genitals to general anasarca, this also has no significance in the prognosis.

The bones of the skull frequently show craniotabes and the scalp hairs are dry and light in colour.

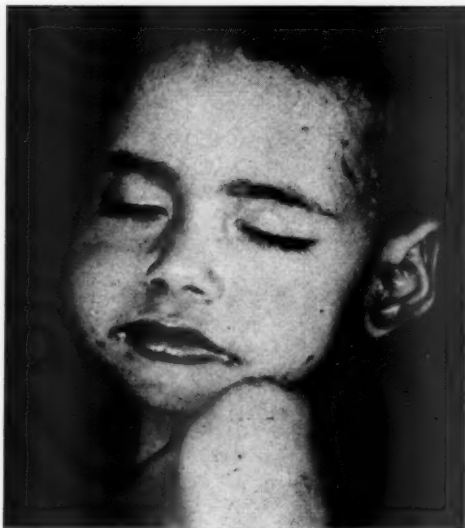


Fig. 3.

Fig. 1-3. Rash 'pellagrous', oedema, lesions around eyes, ears, nose and mouth.

The eyes show angular conjunctivitis with excoriations at the edges, no *Morax Axenfield* bacilli, photophobia & blephorospasm; Conjunctiva injected, red and dry, occasionally, 13 cases, fleshy masses were present over the conjunctiva which in some cases it is subicteric, cornea may be dull and vascularised. Ulcerations and staphylomata are not infrequent. Fundus oculi, normal though sometimes edema of retina may be present.

Lips may be cyanosed. Cheilosis, angular stomatitis with excoriations are present. The gums may bleed and are sometimes spongy stomatitis may be present sometimes with thrush. Tongue is glazed red and papillae atrophied. Teeth eruption not much delayed and are either perfectly normal or decayed and friable. The nose and ears show the same excoriations and ulcerations present around the angles of the mouth. The larynx show paresis of vocal cords (hoarse voice). The submaxillary lymph



Fig. 4. Rash, oedema, trophic ulcers.

glands may be enlarged in the presence of mouth infection. Chest shows harsh puerile breathing with rhonchi and bulbing crepitations.

The abdominal cavity shows two different and definite pictures.

1. Tympanitis is always marked, liver is hard and enlarged may reach 4 fingers below the costal margin. Spleen may be palpable. This may pass to liver cirrhosis with ascites. This picture includes about 15 % of the cases grouped under grade III.

2. In the second group tympanitis is slight and although the liver may be enlarged, it is usually soft and flabby. The spleen may be palpable.

Fig.
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Figs. 5—6. Follicular hyperkeratosis; vit. A deficiency. } The same case.
Characteristic face, rash (Vit. A deficiency), oedema.

The bones may show definit clinical picture of rickets.

Testes in 8 % of cases are incompletely descended.

Hypotonia or hypertonia is present deep reflexes weak or lost, occasionally exaggerated, plantar reflex may be unilateral or bilateral extensor. The temperature curve shows daily fluctuations between 36.2—38 due in most cases to infections, in some cases due to administration of a high protein diet and this usually falls if proteins are withheld.



Fig. 7.



Fig. 8.

Fig. 7. Whole syndrome, grade IV. Wasting, rash 'pellagrous', scalp hairs lighter in colour and density, angular conjunctivitis, blepharitis, photophobia, chelosis, angular stomatitis, excoriation and scaliness around the nose.

Fig. 8. Same syndrome without rash.

Deviations from the usual picture.

In 3 cases features similar to Von Jaechts syndrome (Rickets, enlarged liver, spleen, leucocytosis with premature elements, anemia with premature red cells) were present in addition to the full clinical picture of the subnutritional syndrome (two with pellagrous rash and one free of rash).

Although the chronic subnutritional cases present a facies similar to that of Pink disease, it was only in 2 cases of the whole group that pink discolouration with marked desquamation in hands and feet were noted. The two cases responded to the same treatment as the others.

Tetany may occur in some cases in the form of carpopedal spasm but laryngeal spasm, convulsions never occurred.

Bronchiectasis is present in about 5 % of cases mostly in grade IV.

Laboratory findings:

Urine: normal

Stools: Fermentative, acid, sour smell occasionally offensive. Ascaris in 10 % of the cases, sometimes, blood, pus and mucus. Microscopically and by culture streptococci and staphylococci present.

W. K. out of 197 only one case is positive.

Blood Picture: white cells are increased — 14 000

polymorphs 40 % with premature elements

lymphocytes 52 %.

Red cells 4 millions.

Blood calcium: between 9—8 mgm/100 cc plasma.

Analysis of symptoms in regard to the possible deficiencies on clinical grounds.

Wasting and anorexia are the result of multiple deficiencies, mainly Vit B complex Vit C, A and D, proteins, parathyroid hormone and other factors present in crude liver extract, as is shown by the response to their administration successively.

The cheilitis present particularly at the angles of the mouth and the similar lesions present around the eyes, anus, labia and scrotum, as well as the glossitis suggest a riboflavin deficiency. Bacteriological examination showed the presence of added strept & staph infection at these sites.

The conjunctivitis with pericorneal injection and progressive vascularisation of cornea from out inwards eventually opacity of the cornea, suggest also a riboflavin deficiency. The anorexia, lassitude, glossitis, dermatitis, diarrhea, nausea and vomiting, the anxious distressed facial expression suggest nicotinic acid



Fig. 9. Pre-ascitic stage of cirrhosis, marked tympanitis, liver hard and enlarged; no fluid on aspiration. (In 3 months fluid is present, cirrhosis of liver with ascites). Rash is present.

deficiency. The anorexia, the bleeding gums, the presence in some cases of pains & tenderness around the knees and ankles as well as the marked improvement of these symptoms on administration of Vitamin C suggest Vit C deficiency.

Loss of weight, motor weakness, hyperaesthesia, tenderness of calf muscles, the general irritability, the hoarseness of voice (involvement of recurrent laryngeal nerve), mild opisthotonus,

the loss or weakening of the deep reflexes, all suggest Vitamin B deficiency.

The photophobia and failure of lacrimation with corneal perforation, hyperpigmentation, xerosis and fleshy masses in conjunctiva as well as the chronic tracheitis and bronchitis with interstitial pneumonia and bronchiectasis in some cases and the defective dentin and enamel, all suggest Vitamin A deficiency. Hyper keratosis due to Vitamin A deficiency not described in infants under 3 years of age was observed in two cases of the series aging $1\frac{1}{2}$ and 2 years.

The presence of Rickets clinically and by X-Ray suggests Vitamin D deficiency and shows that rickets may be present with wasting diseases, a fact not realised by many.

The dehydration suggests disturbed metabolism of sodium and chlorine as well as impairment of suprarenal function. Administration of sodium chloride to these cases may preprecipitate edema although they show better appetite and respond readily to treatment. Hoarseness of voice is possibly due to metaplasia and infection of the mucus membranes due to Vitamin A deficiency as well as recurrent laryngeal nerve paresis due to Vit B₁ deficiency.

The edema could be explained by hypoproteinoemia, B, deficiency and possibly administration of excess of sodium chloride. It should be observed that lesions of the mucus membranes may show evidence of low grade infection superadded to the various deficiencies.

Tetany: develop usually at a blood calc level of about 7 mgs/100 cs. In this syndrome tetany usually develops at higher levels viz about 8 mgm/100 cc plasma. Possibly this is due to poor assimilation of the calcium in the tissues as well as increased demand due to the presence of infections. Disturbance of the parathyroid & changes in the acid base equilibrium may play a part. Administration of enough calcium, phosphorus and Vitamin D does not cure tetany in these cases while parathyroid gland tablets alone by mouth relieve it within 24—48 hours.

The hoemorrhagic lesions in the skin and mucus membranes are probably due to Vit K deficiency and Vitamin C deficiency

although tourniquet test is negative. As the administration of ox stomach to these patients causes hoemorrhagic lesions, so it may contain a haemorrhagic factor. (This factor is not present in Hogs stomach.)

Blood in stools may be due to dysentery, Vit C or K deficiency or possibly deficiency of P. A. F. (Permicious anemia factor) or other factors present in crude liver extract and not in ox stomach.

The fact that crude liver is very effective in treating these cases, much more so than B complex and its being in some cases indispensable as well as the fact that in advanced cases, there is evidence of subacute combined degeneration suggest a deficiency in the P. A. factor and possibly other factors present in crude liver such as folin acid, biotin, inositol etc.

The possibility of a deficiency in the P. A. factor is further favoured by the fact that the administration of Hogs' stomach is followed by marked improvement not noted to any degree with ox stomach and the difference between the two, is the presence of P. A. factor in the first and its absence in the second.

It is probable that correction of Vitamin deficiency will cure the early cases, later, due to the affection of the internal organs something as the P. A. factor will be necessary before the Vitamin can work. Later still when the endocrine functions have been affected, factors as parathormone and other hormones will be necessary before either the P. A. F. or vitamin administration can be of value.

In this connection it has been observed¹ that rats kept for long time on a nicotinic acid deficiency diet, develop a peculiar syndrome which quickly improved on crude liver extract but does not respond to nicot acid.

It has been observed in following up the cases reported in this series that patients in the preascitic stage of liver cirrhosis showed a similar response. 60 % of those followed up with no active treatment developped ascites, 40 % of those treated on a proper diet and Vitamin B complex only, developped ascites. While

¹ Cooperman, J. M. McCall, K. B., Rengamer, W. R., and Elevehjem, C. A. *J. Nutrition* 32, 37, 1946.

only 30 % of those receiving crude liver extract in addition, developed ascites.

Outline of treatment.

In early cases administration of a high protein diet with gradual addition of fats and carbohydrates together with the administration of deficient Vitamins is enough. The quantity and quality of the diet should correspond to the weight of the child rather than its real age.

Anorexia in grade III does not respond to nicotinic acid or Vitamin B₁ administration, but contrary to Gillmans¹ view it is cured by Vitamin B Complex. However administration of crude liver extract together with Vit B complex improves the condition, markedly whereas its administration in group IV Cases is the only hope we have for cure. Further its administration in still more advanced cases would be of no avail and the child will continue on wasting until it dies.

The combined administration of crude liver and B complex enhances greatly the action of the former contrary to Gillman's statements. Administration of liver extract is not necessary for a longer period than two weeks. Improvement quickly appears and if stopped it usually continues smoothly on B complex together with proper dieting and Vitamins A, C, and D.

Administration of Hogs stomach is said to be more efficient «Gillmans» than the crude liver extract. However trial of ox stomach in treatment together with Vitamin B complex made the condition worse, diarrhoe, hoemorrhages and petichoe occurred.

It has been observed by some authorities working on animals as regards the B group that the treatment with the specific deficiency alone predisposes for the appearance of other factor deficiencies within the same group. This phenomenon was not observed in our cases through administration of one factor alone make the general condition worse.

The same outline of treatment followed in grade IV cured the

¹ Gillman, T., Gillman, J. Infantile Pellagra, J. A. M. A., volume 129 No. 1, September 1, 1945, p. 17.

cases of pink disease and Von Jaecsths' syndrome. Addition of Parathyroid to a case of pink disease improved it marvelously.

Parathyroid Hormone as a factor in treatment.

The action of parathormone in letary led us to try it in severe cases. It was found that its administration in these cases made them respond much more quickly and favourably to crude liver and other factors. And in grade IV an initial treatment with parathyroid hormone allowed a better ground for the crude liver to work.

In cases with undescended or incompletely descended testicle the administration of gonadotropic hormone resulted in a marked improvement in the general conditions of the patient. Possibly if tried in severe cases (as well as other hormones) it may be of value.

Summary and Conclusion.

1. A condition, presenting the following manifestations, is described
 1. Athrepsia, marasmas
 2. Infantile pellagra
 3. Cirrhosis of Liver
 4. Pink disease
 5. Syndrome simulating Von Jaecsth's ie, rickets, erythroblastosis leucocytosis with premature elements with enlarged liver and spleen.
2. A detailed description of the various stages of the condition is given. It is proved that all the cases, as are seen in Egypt, pass through similar stages indicated by wasting with or without:
 1. Pellagrous rash
 2. Cirrhosis of the liver
 3. Pink disease or
 4. Syndrome simulating Von Jaecsth's
3. An analysis of the clinical symptoms is given which points clearly that the deficiencies are both multiple & varied.

4. The treatment in the various stages of the condition consisted of
 1. Early cases respond to correction of diet.
 2. Later, liver extracts improve the condition markedly
 3. Later the liver extract fails and trial of endocrinal preparations particularly the parathyroid is promising.
5. It appears that after the condition has passed through a primary deficiency syndrome, secondary changes lead to endocrine dysfunction which can only be corrected by appropriate hormone preparations together with an adequate diet.
6. The rôle played by the P. A. factor and by the parathyroid preparations in connection with the syndrome is discussed.

So-called infantile pellagra is, in my opinion, one of these subnutritional manifestations & not a single entity. Photos illustrate this statement clearly.

Los Estados Carenciales en Mexico.

Analisis de 500 niños Avitaminosicos del Hospital Infantil de Mexico.

Por **J. G. Pagola**, Mexico D. F., Mexico.

(Summary.)

A study based on 500 cases, with several deficiencies, seen at the Hospital del Niño of Mexico City is presented.

The main cause was a diarrhea that lasted for months because of lack adequate treatment because of the ignorance of the parents.

Protein deficiencies were present in 100 % of the cases; of these, 31 % corresponded to the first degree malnutrition; 50 %, to the second degree; and 20 %, to the third degree. Nutritional edemas were present in 78 % of the cases; 41 % were of the first degree, 29 % of the second, and 5.4 % of the third degree. The total blood albumins were low in 90 % of the cases. In 75 % of them, the values were between 4 and 7 grams; and in 25 %, they were a little above 7 grams. The serum albumin, in 60 % of the cases, was below 3 grams; and in 30 %, it was between 3 and 4

grams. The serum globulin was below 3 grams in 60 % of the cases; and between 3 and 4 grams, in 30 % of them.

The deficiency phenomena by lack of vitamin A were found in 90 % of the cases from which, 78 % had a beginning of xerosis; 7 % had xerophthalmia with corneal ulcer; 12 % had keratitis; Bitot's patches were seen in 1.3 %; follicular hyperkeratosis was found in 8 % of the cases. The study by means of the biomicroscope revealed diminished humidity of the conjunctiva in 90 % of the cases; diminished brilliancy in 70 %; epithelial thickening in 90 %; and wrinkles in 58 %. The blood titres of vitamin A and carotene were as low as 10 to 20 units per 100 grams.

A thiamine deficiency was found in 100 % of the cases; anorexia and diarrhea, also in 100 %; vomiting in 50 %; generalized hyperesthesias in 70 %; lack of patellar and Achilles tendon reflexes in 50 %; polyneuritis in 50 % depression in 100 %; irritability in 100 %; diminished physical and intellectual powers in 100 %; edemas in 75 %, but these were rather related to the hypoproteinemia; cardiomegalia in 1.3 %; heart murmurs in 1 %. The data of the electrodiagnosis and chronaxia are the following:

a) A reaction of incomplete degeneration in the upper limbs, of bilateral distribution, and symmetrical, of distal predominance. — b) The reaction of degeneration was seen especially in the lower limbs where the most affected muscles are the flexors. — c) In the little advanced deficiency states, the only finding was a hypoexcitability to the electrical stimulus (1st. and 2nd. degrees), without reaction of degeneration. — d) In none of the cases seen with reaction of degeneration was there any paralysis. — e) In the advanced cases of avitaminosis, the chronaxia was greatly increased. — f) Besides, there was hyposensibility to the electrical stimulus, both galvanic and faradic.

The avitaminosis by riboflavine deficiency was found in 90 % of the cases. Cheilosis at the angles of the mouth was present in 88 %; fissures at the sides of the mid-line, were seen only in advanced cases; intense glossitis with smooth and red tongue; in 60 %; slight lesions of the tongue, in 30 %; nasal dryness, in 18 %; maceration of the perineum in 10 %; keratitis in 12 %, but asso-

ciated to lack of vitamin A; engorgement of the circumcorneal veins in 62 %; and alterations of the nails in 6 %.

Nicotinic acid deficiency, with pellagrous manifestations were seen in 100 % of the cases. The symptoms found were, scaly skin in 100 %; dry skin in 99 %; brittle hair, easy to pull off, with alterations in its pigmentation, in 90 % where 90 % had dry hair, 60 % had hair easy to pull off, change in color 70 %, gray hair in 2 %. Pellagroid erythema in 67 %; pigmentary hyperkeratosis in 70 %; flushed lips in 80 %; erythematous lesions of the perineum in 10 %; chronic pneumonitis with permanent infiltrations in 15 %; abdominal distention in 35 %. The hematologic alterations found were, nutritional anemia in 80 %; hypoplastic anemias with leukopenia in 7 %; hypoplastic anemia with a diminution of all the elements including platelets in 5 %; thrombocytopenic purpuras in 5 %; cachectic purpuras in 1.6 %. — Discrete ascorbic acid deficiencies were seen in 100 % of the patients. In their dietetic history, all of them had a lack of intake of vitamin C for months. The titre of ascorbic acid in the blood gave values under 0.6 milligrams per 100 grams. The typical scurvy was rare; it was seen only in 1 %. Epistaxis were seen in 5 %; gingivitis with hemorrhages in 35 %; petechiae and ecchymoses in 15 %; urine with red cells in 7 %; rheumatoid pains, that yielded with ascorbic acid in 1 %; frank radiologic lesions of scurvy in 1 %.

A vitamin D deficiency was rare, and the symptoms of rickets were moderate. Only 4 % showed sufficient signs to support the diagnosis of active rickets. Sweating of the head was present in 2.7 %; muscular weakness and anemia, in 100 %, but related to other avitaminosis; rachitic rosary in 7.6 %; keeled chest, in 4.5 %; craniotabes, in 0.4 %; delayed closure of fontanelles, 3 %; alterations of the bones revealed at the X-rays, 4 %; increase in phosphatase, in 3.5 %; diminution of calcium in 3 %; diminution of phosphorous, 2 %.

Calcium deficiency was also rare. Only 1 % of the patients had tetany.

The association of avitaminosis with other diseases was found with the following incidence: parasitization, 21 %, where 8.4 %

was by ascaris; trichuris, 5 %; lamblia intestinalis, 4.9 %; necator, 3.2 %. — Bloody mucous colitis, 14 %; suppurative otitis, 21 %; congestive otitis, 9.2 %; bronchopneumonia, 22 %; toxic diarrhea, 10 %; glomerulonephritis, 6.5 %; malaria, 2.7 %; pneumonia, 1.3 %; scabies 1.3 %; mastoiditis, 1.6 %; typhoid fever, 1.6 %; thrush, 1.6 %; prurigo, 1.6 %; whooping cough, 1.5 %; encephalitis, 1.5 %; lung abscess, 1.4 %; intestinal occlusion, 1.7 %; umbilical hernia 1.6 %; intussusception 1.5 %; eczema, 1.6 %; hydrocele, 1.7 %; amebic colitis, 1.5 %; suppurative appendicitis 1.3 %; hypochromic anemia, 19 %; hypoplastic anemia, 7.2 %; thrombocytopenic purpura, 5 %; primitive cicatricial lung infection, 10 %; tuberculous meningitis, 2.6 %; tuberculous bronchopneumonia, 2 %; blepharitis, 1.2 %; impetigo, 1.3 %; pneumothorax, 1 %; cachectic purpura, 1.6 %; hepatomegalia, 2.7 %; splenomegalia, 2.7 %.

The mortality was close to 50 % in spite of the intensive therapeutics employed.

Therapeutics was begun with a milk diet of high proteins using calcium caseinate, powdered half skimmed milks, amino acids orally and parenterally. As soon as the diarrhea gave way, the diet was changed for a balanced cow's milk formula, eggs, meat, particularly viscera, vegetables, fruits, whole wheat bread, butter, etc. Blood transfusions were routinely made at the dosis of 10 to 20 grams per kilo of body weight and per day. Vitamin A was given at the dosis of 100 000 units per day. Thiamine, 10 to 30 milligrams. Riboflavine, 10 to 25 mgms. Nicotinic acid, 100 to 200 mgms. Ascorbic acid 100 to 500 mgms. Vitamin D, 5 000 to 10 000 units per day. Brewer's yeast, 15 to 30 grams daily. Total liver extract 5 to 10 c. c. daily. Folic acid, 5 to 10 mgms. Ferrous sulphate 0.5 to 1 gms. Ammonium iron citrate, 1.5 to 3 grams.

Avitaminosis in Dutch Children in Concentration-Camps.

By **S. van Creveld**, Amsterdam, Netherlands.

Next to the thousands of Dutch children who in recent years suffered or fell indirectly prey to the barbarous Hun's lust for

blood and vengeance and whose medical conditions were discussed in one of the lectures at the opening-session of this congress, there were two other groups of children who have been collected in concentration-camps, respectively in Holland and in the Dutch Indies.

The group in Holland, comprising about 20 000 babies and older children, principally Dutch Jewish children, were concentrated with or without their parents in two camps on Dutch soil (named »Lager Westerbork» and »Auffanglager Vught»). From these camps, the children who survived were after a longer or shorter stay there, for about 90 % conveyed from Holland to Poland by means of cattle-trucks. On their arrival in Poland they all were gassed or knocked down by living beings called men or women.

I have been able to observe these children before their death in both camps on Dutch soil. Especially in Vught the children lived in most unhygienic surroundings and got a very insufficient quantity and quality of food. They were moreover subjected to a series of infections. Human imagination is not vivid enough to invent the cruelties committed here under supervision of men, who had once sworn the oath of Hippocrates, against the children of a country, which for many years could be proud to have the lowest mortality rate for babies of the whole world.

The nutritional state of all these children was abominable. When they died — and especially the death-rate of the babies was extraordinarily high — the mothers were for a long time forbidden to be present at the bedside of their children.

The time spent in this concentration-camp has for the greater part of the children only been short: some weeks to some months. Then they died or were transported to Poland. Still it is of importance that among the varied clinical pictures which these children showed, next to severe emaciation and edema, clinical avitaminotic symptoms did occur. Especially symptoms of vitamin C-shortage and slight symptoms of ariboflavinosis and of pellagra were noticed. A closer study of the conditions by investigation of blood and of urine was of course forbidden, like all laboratory study of blood and of urine.

A nearer study in many aspects could be made in the second group of Dutch children which passed through concentration-camps. This group concerns the children, who stayed for two to three years in concentration-camps on Java. In that period the food became steadily worse. From a report of Dr. J. H. DE HAAS and H. POSTHUMA, it appears that both the caloric value of the food and the protein-content decreased steadily. Moreover the food was limited in such a way, that finally it practically consisted only of carbohydrates and water. Therefore it is small wonder that alimentary edema developed in the greater part of the children and often deficiency-symptoms, especially different stages of pellagra.

All was promoted by numerous infections and diarrhea, of which these children suffered in the camps. Further it must be considered that the children in the Indian camps had to work intensively. After the defeat of Japan the majority of the children got a better diet, sufficient vitamins and the necessary drugs. It took, however, still a fairly long time before these children were transported to Holland and during the voyage part of them still suffered from severe infections. We had the opportunity of observing a fairly large number of these children.

As regards the avitaminotic symptoms and the consequences of an insufficient quantity or quality of food, it had been noticed in the camps on Java that the bad food especially had caused edema and a general malnutrition; only in a smaller degree so-called specific deficiencies had appeared. The general character of the edema, with absence of other symptoms of beri-beri, made it very improbable that one had to deal with edema based upon shortage of B. Symptoms of pellagra and ariboflavinosis were frequent.

It is noteworthy that in a large number of these children after their arrival in Amsterdam, avitaminotic symptoms were very marked, notwithstanding the fact that for weeks and months they had received already again good food. This fact partly can be explained by the infections through which the children passed, partly by the increased demand for vitamins when the children got better food. Among the clinical symptoms which the children

showed after their arrival in Amsterdam and which could be considered to be deficiency-symptoms, were anomalies of the lips, of the tongue, of the skin and mixed symptoms.

Further several of these children, born in the tropics, showed rachitic symptoms. A fairly frequent symptom was also tenderness of the muscles of the calf on pressure, with abnormal reflexes of feet and knees.

The symptoms of the lips consisted in cheilosis, fissures and crusts on the lips and an angular stomatitis.

The symptoms of the skin consisted in an intensive desquamation, seborrheic dermatitis, localised especially in the face, on the forehead, in the temporal regions and in the naso-labial regions. There were further symmetric areas where the skin was dry, darkly pigmented and sometimes also showed a distinct hyperkeratosis. Some children had a vaginitis and an enlarged liver. Eye-symptoms which would be characteristic for ariboflavinosis were absent! The symptoms, especially those found on lips and tongue, corresponded as well to the syndrome of ariboflavinosis as to that of pellagra. The anamnesis did not point especially to the shortage of one kind of vitamin.

The metabolism of these children was studied in different directions. Only in a single case the total protein content of the blood plasma was found to be decreased. In several cases an important increase of globulin was present and at least temporarily a strongly positive flocculation test was found.

Liver enlargement was present in several cases. Malaria parasites were rarely found.

The treatment of the deficiency-symptoms consisted in the administration of a mixed diet with a total vitamin-B complex. The rapidity with which the deficiency-symptoms of skin and mucous membranes disappeared, was remarkable. Parallel to this, the abnormalities in the protein-spectrum usually disappeared and a positive flocculation-test became negative. In some cases, however, the enlargement of the liver as also the changes in the blood remained for a long time, pointing to a more intensive parenchymatous damage of the liver.

Citric Acid and Rickets.

By **Erich Rominger**, Kiel, Germany.

The discovery of the antirachitic effect of citric acid by American authors (Shol, Hamilton and Dewar, Hathaway and Meyer) prompted us to investigate the mechanism of Vitamin D and this chemically simple compound in the hope of developing a new antirachitic principle.

My first experiments in 1944 were just a crude beginning. In them I used large amounts of sodium citrate in men and animals. Even very severe forms of rickets were cured in 3 to 5 weeks on daily doses of 20, 30, or 50 grams of sodium citrate.

Intensive experimental and clinical investigations by the Swiss authors Glanzmann, Meier and Walthard not only confirmed the preventive and curative effect of citric acid in rickets in man and animals; they obtained in several cases excellent therapeutic results even with relatively small amounts. However, the Swiss authors sometimes encountered failures and incomplete cures, and we face also the difficulty of explaining the lack of effects with the citric acid milks of Mariott frequently used in Europe.

In view of this situation, we have studied in Kiel chiefly the mechanism of action of citric acid, and I shall present our observations briefly, which, though they cannot yet explain the citric acid effect beyond doubt, offer a satisfactory hypothesis and furnish some light on the pathogenesis of rickets.

Let us begin with the simpler problem of prevention and cure of McCollum rickets in rats, the development of which depends exclusively on the ratio of P:Ca in the diet, in contrast to the spontaneous human rickets. A surplus of P over the Ca will cure the rat rickets immediately, while too little P causes rickets. The loss of P in experimental rickets is not the consequence of an inadequate ability to absorb P, but the result of an augmented formation and increased elimination of tertiary calcium phosphate, which occurs due to the excess of Ca in the intestines. We thus deal with a real «intestinal rickets». If we add citric acid to the

McCollum diet, P excretion through the intestines stops immediately, the hypophosphatemia disappears, Ca absorption is improved, and — most important — calcium is delivered to the sites of bone formation in a form obviously specially suited for the purpose.

From this we learn that the addition of ionized calcium not only fails to benefit the growing organism, but actually harms it in Vitamin D deficiency. In this condition the organism promptly excretes this excess of non-utilizable ionized Ca as a defence mechanism. This results in insufficient calcification of the growing bone, i.e., rickets. Citric acid transforms ionized Ca into a «not-ionized» form of calcium by forming a complex salt of citric acid-calcium. The calcium loss by intestinal excretion is thus inhibited, the bone calcification is furthered, and the rickets cured.

The conditions in human rickets are more complicated. Here the origin and cure of rickets has no definite dependence on the Ca:P ratio in the diet. By observing the mineral metabolism before, during, and after huge doses of Vitamin D (Rominger—Meyer—Bomskov), we saw that the rachitic metabolic disturbance is obviously characterized by demineralization of the skeleton, in which loss of P precedes that of Ca. During healing, the phosphorus remineralization again precedes the Ca, so that the phosphorus disturbance seems to be primary.

Nowadays, however, on the basis of our citric acid cures, we know that this is not the case, and that in rickets the *Ca metabolism is primarily disturbed* while changes in the phosphorus economy must be considered as a secondary regulatory measure of the organism. With decreased Ca retention, an immediate increase in production of parathyroid hormone occurs in order to maintain a fairly constant normal serum Ca level, as shown by Albright and coworkers. Urinary excretion of P is increased to such an extent that the quotient of Ca and P-ions is so deranged that the formation of apatite is finally no longer possible. The maintenance of serum calcium continues at the expense of Ca in the skeleton.

Hypophosphatemia in human rickets is caused right at the beginning by increased P diuresis due to a counter-regulation of

the parathyroid and is a consequence of primary insufficient Ca retention.

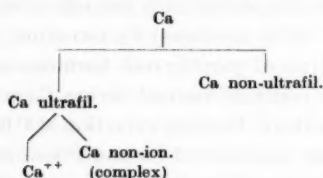
Cure of rickets with citric acid is owing mainly to the formation of a calcium citrate complex salt. The complex Ca citric acid compound improves Ca retention by no longer permitting any excretory losses; on the other hand, being an anion, it provides the form of Ca necessary for transportation and deposit — that is, the proper form for bone apatite.

The effect of Vitamin D must be similar, since the organism reacts in the same way to Vitamin D administration as to citric acid. Vitamin D also influences Ca economy.

The essential feature in the case of citric acid therapy is the formation of a citric acid calcium complex. We have attempted to clarify as far as possible the structure of this compound.

Since the time at my disposal is short, I can only report briefly on the work, and, for the rest, merely refer to our paper, which will appear soon in the *»Zeitschrift für Kinderheilkunde»*.

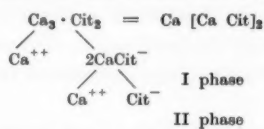
Taking into account the solubilities of the blood Ca salts, we find that the Ca content of the blood is much higher than could be expected from these physical constants. This can be explained only by the presence of non-ionized calcium in the blood and by the fact that this form plays an important rôle with regard to the dissolving capacities of the blood. Today we distinguish between several fractions of calcium in the blood, i. e., ionized Ca, ultrafiltrable, non-ionized Ca, and also Ca bound to protein colloids, which is not ultrafiltrable, as indicated by Figure 1.



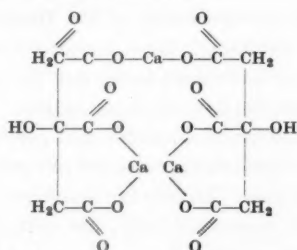
Hastings has shown that calcium salts in citric acid solutions, as in the blood, are dissolved far beyond their products of solubility in non-ionic form, i. e., in complex salts. When Marlow injected sodium citrate into the blood of rabbits, most of the ionized cal-

cum disappeared almost immediately, because a practically undissociated Ca compound, a citrate complex salt, was formed. The animals died in convulsions due to hypocalcemia. The same process, namely, the formation of citrate Ca complex, evidently is used to prevent coagulation by adding sodium citrate to a blood sample. We have performed a whole series of similar experiments, which show unequivocally that citric acid is capable of forming practically undissociated complex salts with the ionized Ca of the blood.

According to our experience to date, it seems improbable that this Ca citrate complex also contains phosphate and carbonate ions. It seems much more probable that our complex is nothing else than a Ca citrate anion, as described by Hastings in 1934 — a Ca citrate anion formed by dissociation of a Ca ion from tertiary Ca citrate. The tertiary Ca citrate dissociates in two steps, as demonstrated by the scheme illustrated in Figure 2.



The Ca citrate complex in question apparently is that formed during the first step of the dissociation and, according to Hastings, has the following structural formula:



We now come to a question of great practical importance, that is, why is a child fed with cow's milk especially prone to develop rickets, even though cow's milk contains four to five times as much calcium and twice as much Vitamin D as human milk?

Even in cow's milk the Ca content is higher than to be expected according to the dissolving capacity of its most important Ca salts. A considerable fraction is kept in solution in colloidal form by adsorption on proteins and other substances. If for theoretical purposes we consider milk as a simple solution, the citric acid in cow's milk, in contrast to human milk, is not sufficient to keep in solution all of the Ca in the form of the postulated Ca citrate complex. At least 4.3 grams citric acid are needed to keep in solution 1 gram of Ca in the form of the complex salt; that is, the quotient citric acid : Ca should not be lower than 4.3. In testing human milk, we find that its ratio of citric acid to Ca corresponds approximately to the minimal value 4.3. (See Figure 4.)

	Ca	Citric Acid	Quotient Ca/Citric Acid
Cow's Milk	0.126 %	0.25 %	2
Human Milk	0.028 %	0.12 %	4.3

To make cow's milk effective in rickets, it would seem simple enough just to increase its inadequate citrate content. But this simple correction of cow's milk to eliminate its rachitogenic effect does not work.

This is shown by the fact that a reliable anti-rachitic effect cannot be achieved in citric acid milk even by adding about 4.6 grams crystalline citric acid per liter of cow's milk. The reason for this is explained by physicochemical calculations. Equimolar amounts of citrate suffice for the formation of the Hastings complex only in *highly* dilute Ca solutions. With higher Ca concentrations we need a huge excess of citric acid to inhibit the appearance of free Ca-ions, in line with the law of mass action. According to our calculations, about 40 grams of citric acid per liter are needed to keep in solution the high calcium content of cow's milk in the form of the Hastings complex. Equimolar amounts of citrate, such as are actually present in human milk, are sufficient. Thus, cow's milk has rachitogenic action not *in spite of*, but *because of* its high calcium content. Since such high amounts of citric acid are impractical, one must reduce the calcium content of cow's milk, in order to get along on smaller amounts of citric acid. We have developed such a preparation of milk, low in mineral content, con-

sisting essentially of one-third milk, plus whey albumin, carbohydrate, and fat. For such «one-third» milk product, poor in Ca, only 1.75 gram citric acid per liter is needed. This milk is no longer rachitogenic. Only further experiments can show whether the administration of a citrate, in the form of the Hastings complex, will cure rickets as well as prevent it. We believe we have opened a path which may make it possible to achieve the three main effects of citric acid in preventing rickets by the use of Ca citrate compound, active as anion, that is:

- 1) improvement of Ca absorption in the infant's intestine,
- 2) unobstructed transport of Ca in the blood to the sites of bone formation, and
- 3) furthering of Ca deposition.

It is tempting to assume that Vitamin D is merely instrumental in forming a Ca complex salt. Since the organism itself can form citric acid (Breusch), it would seem not impossible that a Ca citrate complex may play a physiological rôle at some point in the Vitamin D activity.

We may draw two conclusions on the basis of the citric acid investigations:

1) Rickets is based on a primary disturbance in calcium metabolism, or, expressed in another way, lack of Vitamin D causes a skeletal disease of calcium insufficiency.

2) Vitamin D and citric acid prevent and cure rickets both probably by formation of Ca complex salts, which no longer have cationic properties.

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Section 5—Insect and other Vectors of Disease

Protozoal Diarrheas in Childhood.

By Dr. S. E. Berman.

Department of Pediatrics Rotschild Hadassah University Hospital, Jerusalem,
Palestine.

The successful adjustment of an organism to a parasitic existence usually derives from the following facts: The parasite has a single ultimate host species, given favorable conditions of spread it infests large numbers of individuals of this host species; it produces manifest signs of disease either rarely or only for short transient periods with longer symptomless pauses in between. The symptomless host-parasite relationship should, however, be looked upon as a mutual adjustment which no matter how good it may be, is one of greater or lesser instability. Knowing as little as we do both of the biochemical activity of the protozoal cell and of the manner in which the host reacts to the parasites, we cannot even speculate upon the causes which disturb the host-parasite adjustment and which change the symptomless state to one presenting symptoms. As far as the host is concerned, we may possibly assume that factors leading to a reduction of general or local resistance will favor the upsetting of the host-parasite balance, factors such as age, malnutrition, previous general disease or one affecting the intestinal tract. The importance of age and perhaps of malnutrition also as well as previous gastro intestinal disease is exemplified in *Giardiasis*. In our experience *Giardia lamblia* is the chief cause of protozoal diarrhea in infancy. Our youngest case was a 17-day old infant, breast fed only. Most of the infants in the pediatrics wards of the Hadassah Hospital in Jerusalem come from the under-privileged classes of

the population, and so we cannot be certain whether undernourishment or previous diseases of the intestine are factors favoring the appearance of symptoms in Giardiasis; we do, however, strongly suspect that these are contributing factors. On the other hand we are convinced that giardiasis can help precipitate manifest deficiency states in the affected infants.

The intestinal symptoms of giardiasis in infancy consists of what we call silent diarrhea in contrast to the violent bacillary diarrheas. The infant passes softer stools containing much mucous. Only rarely is the stool only mucous of the greenish tinge described by Brumpt. The number of stools is also increased. This alternates with periods when the infant appears relatively well. The condition continuing for weeks and months leads to undernourishment, and as I have said may even precipitate manifest deficiency symptoms.

The diagnose is made by the finding of giardia either vegetative or cystic in the stool. In our experience the infant suffering from giardiasis need not always pass either vegetative or cystic giardia; we have had cases where we found the organisms only after 10, 12 stool examinations in spite of the fact that the patient had abnormal stools all of the time, failed to gain in weight on an adequate diet, and responded favorably to specific treatment both as regards his general and local condition. The mucous passed in the stool is much more likely to contain the parasite; it is remarkably cell-poor so that if we find an abundance of cells we assume a combination of giardia and bacillary diarrhea and treat the cases accordingly.

Our treatment in addition to diet consists of the administrative of atabrine, 5—7 mgm. per kilo per day for five days. If we assume a combined infection with a bacillus we give one of the sulfa preparations together with the atabrine; usually sulfa-suxidine and continue with this treatment as long as 12—14 days; we found that with shorter treatment relapses of the diarrhea were more common.

Three negative stools for giardia is the criterion of a successful cure. We know that this is not enough but in scores of cases we have succeeded in obtaining three negative stools after the

above atabrine cure and we feel justified in assuming that it is very effective.

After returning to the home many infants are reinfected with giardia; the majority either show no symptoms or only mild ones. We believe that the increased age and improved nutritional state protects them from the effects of reinfection.

Entameba histolytica. Except for one case, eight months of age with an immense amebic abscess of the liver discovered at autopsy we have seen no case of infection with *entameba histolytica* in the first year of life. With increasing age we find amebae increasingly often. Considering that our infants come from home environments probably highly infected with amebiasis, also considering that giardiasis is very common among them and that the methods of transmission of the two parasites are most likely quite similar, the absence of amebiasis in the first year of life is surprising. We assume, and our assumption is supported by the work of Adler and Fonor, that the intestinal environment in infancy is unfavorable to the establishment of an amebic infection. Adler and Fonor found a marked amebicidal action of the normal stool — very pronounced in the few cases of infant's stools examined.

The symptoms are similar to those in adults, and range from no symptoms through indefinite abdominal distress to actual amebic dysentery. The last is likely to be more common and more severe when the ulceration is close to the anus. Liver involvement is, however, extremely rare in childhood.

The diagnosis is extremely important and we rely only on the microscopic examination of one or many stools, usually after a saline purgative. Occasionally we culture the stool in doubtful cases. Proctoscopy with the microscopic examination of the material obtained is frequently necessary.

Our treatment consists of emetine for the control of acute symptoms, 1 mgm per kilo per day, followed by arsenic in the form of carbarom or one of the iodine preparations.

In view of the fact that we have succeeded in controlling the dysenteric symptoms in all cases with emetine only, we are in-

clined to agree with Prof. Adler that a combined amebic and bacillary dysentery is rare.

In the past we had a number of deaths following the injection of emetine in infants. Recalling the rarity of amebiasis in infancy we assume that these children were suffering from bacillary dysentery and that the giving of emetine, a heart toxin, to infants whose hearts were already damaged by the toxins of the dysentery bacilli resulted in these fatalities.

We do not believe in the effectiveness of preparations against cysts, nor, living in a country with a high infestation rate, do we see the need, from an epidemiological point of view, to make a great effort to clear the patient of cysts.

Other protozoa causing diarrhea that we have encountered rarely are *Bulantidium coli* and *Isospora hominis* — the latter is not certainly pathogenic. Kala-Azar associated with diarrhea is sometimes seen. What is more important is the bloody diarrhea seen occasionally in aestivo-autumnal malaria. Mucous and pus are usually absent from these stools. The patients have high fever as a rule. In every case of diarrhea with blood, a thick blood film should be made and examined for malaria.

I have said that the host-parasitis adjustment is potentially unstable and except for proven coprophages, all parasites may give rise to symptoms under the right conditions determined by factors in the host, the parasite, or both; factors as yet unknown. As far as *Trichomonas hominis* is concerned we strongly suspect that it causes symptoms not infrequently. Quite often we have seen a prolonged intestinal derangement in which *Trichomonas* was found in large numbers. Only after a long period of dietary and general therapy was the condition improved. In one case even that failed and only after a course of carbarsom therapy did the infant recover.

It is likely that further investigation will show that a larger variety of intestinal protozoa are pathogenic. While pronounced symptoms may not be common, it is possible that they cause a widespread lowering of the level of health and working efficiency, and, if so, they are worthy of more consideration that we have given them hitherto.

In a hyperendemic area we treat the symptoms only of protozoal infection and do not attempt to eradicate the infection entirely. The chances of reinfection are so great that we consider such an attempt futile. Where the infection is rare determined effort should be made to eradicate the infection in every individual case.

Should investigation show that widespread lowering of the health of a community is caused by these parasites, and should chemotherapeutic agents of better quality be discovered than mass treatment would be worth while. To clarify this and other problems of protozoal infection of the human intestine will require much further study; this effort will be well repaid in the raising of the general health of the underprivileged peoples of the world.

Epidemiology of St. Louis Encephalitis.

By Dr. Russell J. Blattner, Dr. Florence M. Heys, Dr. Margaret G. Smith, and Dr. Albert Miller, St. Louis, Missouri.

Field and laboratory studies have suggested that the epidemiology of St. Louis encephalitis is a complicated one, probably involving two arthropod vectors.

Proved inter-epidemic cases indicate that an endemic focus of the disease exists in the St. Louis area, seventeen cases of acute encephalitis occurring in this area from 1939—1946 having been shown to be of the St. Louis type. All of these cases occurred in the summer months, and the majority was resident in regions of St. Louis County where high per capita incidence of St. Louis encephalitis occurred during the two epidemics (1933 and 1937). In one instance the virus of St. Louis encephalitis was isolated from the bloodstream of an 8-year-old boy who became ill in July, 1945, with symptoms and signs of encephalitis, and who recovered.

Experimental work in the laboratory showed that the arachnid vector, *Dermacentor variabilis*, is capable of being infected with the virus of St. Louis encephalitis by feeding on inoculated animals and likewise of transmitting the virus to normal susceptible

animals by bite. Transovarian passage of the virus in the tick was demonstrated.

The virus of St. Louis encephalitis was shown to occur naturally in the bodies of chicken mites (*Dermanyssus gallinae*) collected in this area during non-epidemic periods. Normal chicken mites raised in the laboratory may be infected readily with the virus by allowing them to feed on chickens with experimentally induced viremia. The mite has been shown to be a potential reservoir for the perpetuation of the virus since once infected, a female mite passes the virus by congenital transfer through the egg and all subsequent stages of development. Culicine mosquitoes are capable of being infected with the virus of St. Louis encephalitis by feeding on chickens with induced viremia. Normal chickens fed upon by infected mites showed a viremia for 24—72 hours after the feeding. Uninfected mosquitoes allowed to feed on such chickens acquired the virus, were capable of transmitting it to other (normal) chickens by bite, and to date have been shown to produce viremia in the hamster by bite. Normal chickens in which viremia was induced by the bite of infected mosquitoes were used to establish colonies of infected chicken mites. These findings appear to indicate that the virus of St. Louis encephalitis is maintained in nature in chicken mites which are capable of producing viremia in chickens by bite. Under favorable conditions mosquitoes can acquire the virus by feeding on such chickens and might be responsible for carrying the infection to human beings.

Sensitivity of Animals (Cats) to Epithelial Virus of Poliomyelitis.

By Dr. G. Salvioli.

Professor of Pediatrics at the University of Bologna.

Some epidemiological observations induced me to believe that besides the monkey, other animals were sensitive to the virus of poliomyelitis.

It is not necessarily true that in spontaneous and experimental

pathology of animals we have to expect a reproduction of nervous symptoms.

Experiments directed by me and carried out in my Pediatric Clinic and Center for Infantile Paralysis at Bologna confirmed such a point of view.

The cat was the animal used in all experiments in collaboration with Dr. Sternini.

The animals inoculated with material (spinal fluid or stool) from patients affected by the disease, or with filtrates of such material, developed serious and lethal pictures.

The inoculations were made with spinal fluids of patients with meningitis due to the virus of poliomyelitis. This material was injected in the cerebral ventricles, into the brain and in the nasal mucosae membranes and conjunctiva.

The stools were introduced into the intestines by duodenal sound and in the rectum by rectal tube.

The filtrates of such stools were used parenterally and in the intestines.

In subsequent passages of suspension of scrapings of intestinal mucosa or filtrates of such material were used and introduced either by way of the intestine or parenterally.

Up to the present we have obtained four (4) passages from one animal to another with symptoms of increasing severity. We have constantly noticed a morbid symptomatology after a very short period of quietness characterized by marked diarrhoea, loss of weight, weakness, tremors, slight fever, followed by death in a few days.

In two of the animals we obtained flaccid paralysis of one extremity.

We did not notice such symptoms in animals inoculated with spinal fluid of normal persons.

The animals which did survive were very few and among them two (2) animals inoculated with scrapings of intestinal mucous membranes of affected animals, which were previously mixed with serum of convalescents from Poliomyelitis.

Therefore we deduce that in the pathogenic material used there is a substance which can be neutralized by serum from con-

valescents. The animals which overcame the infection have shown good resistance to subsequent inoculations of infected material.

On the basis of such limited experiments new ways of study are open to future workers.

The Epidemiology and Pathogenesis of Poliomyelitis must be reconsidered.

We have to consider the tropism of the virus of Poliomyelitis specific for the epithelia and especially for the epithelia of the intestines which at times give symptoms of intestinal disturbances.

The specificity of the nervous system takes therefore a secondary place.

Kala azar in China.

By **Hua K'ang Chow, M. D.**

Department of Pediatrics, University of Minnesota Medical School.

Of the three clinical types of leishmania infection in man, only the visceral form, namely kala azar, has been found to be endemic in China. Up to the present time there has not been a single case of endogenous cutaneous or muco-cutaneous form reported in that country. In 1940, Hoeppli (1), in summarizing the distribution of kala azar, stated that although this disease might exist in west, Central and South China, the endemic areas up to that time were all found north of the Yantze Valley. In some districts as many as five thousand cases may be seen in a year's time. Since the outbreak of hostilities in China in 1937, this disease has appeared in many places where it was formerly unknown and it has increased significantly in areas where it had previously been present.

Transmission of kala azar by direct or indirect contamination is a possibility, although rather unlikely under natural conditions. Both experimental and circumstantial evidence point to sandfly as the insect vector of this disease. Epidemiological, clinical and laboratory studies have shown that the parasites of human and dog kala azar are essentially identical. (2) The heavily parasiti-

tized skin of an infected dog, in contrast to that of a patient, suggests that the dog is a much more important reservoir host.

Kala azar, in China, is predominantly a disease of the younger age groups. However, when the infection is first introduced into a non-endemic area the age incidence tends to correspond to that of the existing population. The incubation period varies widely from a few weeks to many months. Although the majority of the patients present a very insidious onset, a significant number simulate that of a typhoid or malaria. The early symptoms are by no means constant or characteristic. They may be those of general ill health or they may be referable to the respiratory or gastrointestinal tracts. Fever is almost always present, intermittent or remittent, sometimes showing two or three rises in twenty four hours. After a few spontaneous remissions and relapses, nearly all patients will present the classical features of this disease: long continued, irregular fever, enlargement of the liver and spleen, increasing pallor and fatigue and signs of malnutrition. Leucopenia with marked decrease in the proportion of granulocytes is a constant finding. Anemia and thrombocytopenia of varying degree are usually present. Erythrocyte sedimentation rate is always increased. Of the many tests devised on the basis of increased euglobulin content in the blood, the one commonly used in China is perhaps the simplest. (3) It consists of the addition of 0.02 cc. of blood to 0.6 cc. of neutral distilled water. A positive reaction is indicated by the appearance of a precipitate within sixty minutes. It may be present in a few other conditions, although rarely as strong as in the late stage of kala azar. A negative result is not significant in the early phase of the disease. Complement fixation test, while very successful experimentally, has not yet been used extensively in clinical practice.

While a well established case of kala azar usually presents a typical, clinical syndrome, the diagnosis of early cases can be extremely difficult. The one and only infallible criterion is the demonstration of the causative organism. The search of the blood smear is always tedious and often fruitless. Examination of material aspirated from a lymph gland, liver, spleen or bone

marrow has been advocated by various workers. Experience in China has shown that puncture of the sternum is the most practical and the method of choice in all cases. Although parasites are found most frequently in the splenic pulp, puncture of that organ is invariably associated with the possible danger of a fatal hemorrhage. Puncture of the sternum is simple and easy to carry out. Practically no contraindication exists and no special precaution is necessary. It can be performed in early cases with just as much ease and in other diseases with just as much safety. It can be repeated as often as may be considered necessary. The danger of hemorrhage exists only in cases of hemophilia. It is conceivable that the needle may go through the sternum and injure the vital organs below. The use of a specially short needle or one with a rotating guard which can be adjusted in accordance with the thickness of the bone has completely done away with this remote but possible danger. The chance of finding the parasite in the examination of the bone marrow is almost as good as that of the splenic pulp. Furthermore, certain enteric infections, blood dyscrasias and other parasitic diseases which frequently enter into the differential diagnosis of kala azar can often be identified by proper microscopic or bacteriological examination of the same material. Although examination of the smears usually establishes the diagnosis in the great majority of cases, culture of the aspirated material provides a very useful adjunct to the diagnostic procedures. Biopsy of enlarged lymph gland when present is often helpful. Animal inoculation is of no practical, clinical value.

Prior to the use of specific therapy kala azar was a highly fatal disease. The employment of the trivalent antimony compounds has never been popular in China. Ureastibamine, first introduced by Bramachair in 1922, still remains as one of the most potent of all the antimony preparations. When properly administered the cure rate may be as high as ninety five per cent. Toxic symptoms are relatively frequent but rarely disastrous. Neostibosan is the drug most commonly used. It is probably less potent but also less toxic. Given intramuscularly it is not always without local reaction. Solustibosan was the first penta-

valent compound to be prepared in the form of a stable solution. It can be given intravenously, intramuscularly or subcutaneously. It is about as effective as any other preparation and certainly the least toxic of all. It is the drug of choice in children, in ambulatory cases and in massive therapy. Whether concentrated solustibosan or solustibosan suspension in oil has any more to offer or not it is yet too early to say. The introduction of aromatic diamidines undoubtedly constitutes another important advance in the chemotherapy of kala azar. In China, stibamidine has been used with success in patients with idiosyncrasy or resistance to the antimony preparations. Immediate shock like reactions have been recorded. So far, delayed poisoning of the nervous system has not been observed.

Penicillin, while totally devoid of specific action on the parasite in cultures, infected animals or patients, is undoubtedly very useful in treating the frequent and often fatal complications of this disease. Unprecedented success has been noted in cases of kala azar complicated with cancrum oris, agranulocytosis, pneumonia and other secondary pyogenic infections.

General supportive therapy, such as correction of malnutrition, treatment of anemia and proper care of the oral hygiene decidedly contributes a great deal to the prevention of complications and hastens the recovery under specific therapy.

The mechanism of immunity in this disease is still not clear and no satisfactory method of immunization has been discovered. The control of sandfly is notoriously difficult. The recent advances in our knowledge of insecticides, such as the use of D. D. T. (dichloro-diphenyl-trichloroethane) will unquestionably contribute a great deal to the solution of this problem. As yet, it appears that the most effective means of prophylaxis is still the strict supervision of all dogs and extermination of the infected ones plus the massive and continuous treatment of human cases.

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Malaria im Kindesalter.

Von Prof. **Albert Eckstein**, Ankara, Turkey.

Die Malaria spielt im Krankheitsgeschehen der Kinder in den warmen Ländern eine ausserordentliche Rolle. Bei dem chronischen Verlauf dieser Krankheit überschattet Siechtum oder Tod das Leben der Kinder in den endemischen Malariagebieten, in denen bis zu 100 % der Kinder davon befallen sein können.

Der Verlauf der Malaria zeigt in allen Altersklassen vom Neugeborenen bis zum Erwachsenen grosse Variationen des klinischen Bildes, wobei man annehmen darf, dass er umso weniger dem Lehrbuchtypus entspricht, je jünger das Kind ist. Dies hängt von den altersbedingten Reaktionen des Organismus gegenüber den Malariaplasmodien ab, daneben wahrscheinlich auch noch von anderen Faktoren (Massivität der Infektion, der Art der Plasmodien, Häufigkeit der Reinfektion, allgemeinen Lebensbedingungen).

Das dem Lehrbuchtypus entsprechende klinische Bild der Malaria bei den für den Menschen pathogenen 4 Arten der Malaria (*M. tertiana*, *M. Tropica*, *M. ovale* u. *M. quartana*) darf als bekannt vorausgesetzt werden. Es kann, wenn auch seltener, bei Kindern jeder Altersstufe beobachtet werden. Viel häufiger sind die für das Kindesalter charakteristischen Variationen des klinischen Verlaufs, die in das grosse Bild der okulten Malaria einzureihen sind. Neben den von mir in einer Monographie (*«Malaria im Kindesalter»*, Verlag Karger) beschriebenen Besonderheiten sollen hier meine neueren Beobachtungen der angeborenen Malaria in ihren wesentlichsten Punkten zusammengefasst werden.

Man hat bei Kindern nur selten Gelegenheit, das *Prodromalstadium* zu beobachten. Das Froststadium entgeht, namentlich wenn der Anfall nachts erfolgt, fast immer der Aufmerksamkeit

der Eltern. Schüttelfröste kommen bei Säuglingen u. Kleinkindern nur selten vor, dafür als Äquivalent die auch bei anderen Krankheiten zu beobachtenden »Fieberkrämpfe«. Häufig sieht man in diesem Stadium eine abnorme Kühle der Extremitäten mit u. ohne Akrocyanose, gewissermassen einen »Schüttelfrost ohne Schütteln«. Auch das für den Malaria-Anfall so charakteristische »Hitzegefühl« entgeht, namentlich bei jungen Kindern, unserer Kenntnis. Das »Stadium des Schweisses« ist meist gut ausgeprägt, führt aber bei Säuglingen mit stark durchnässten Windeln leicht zu diagnostischen Irrtümern, zumal das Schwitzen in den heissen Ländern nicht auffallend ist. Der Fieberverlauf kann den bekannten Schemen entsprechen, ist aber, namentlich bei jungen Kindern nicht selten uncharakteristisch u. entspricht nur andeutungsweise den für die einzelnen Malariaformen typischen Fieberformen. Mischinfektionen mit verschiedenen Plasmodien u. mehrfache Infektionen mit demselben Plasmodium (Infektionen mit mehreren Generationen) beeinträchtigen den typischen Fieberverlauf.

Die für das Kindesalter besonders charakteristischen Sonderformen der Malaria sind folgende:

1) *Die okulte (symptomarme) Malaria.* Im Gegensatz zu den als »Lehrbuchtypus« bezeichneten normalen Verlaufsformen ist hier der Mangel an charakteristischen Symptomen das besondere Kennzeichen, so dass die Diagnose der Malaria häufig nur zufällig gestellt wird. Oft sind es nur Angaben über ein Nicht-Gedeihen des Säuglings, sogenannte nervöse Beschwerden älterer Kinder, die vor allem nachts auftreten, eine bei der Untersuchung unerwartet festgestellte leichte Vergrösserung der Milz, eine stärkere Anämie, die den Arzt veranlassen, eine Blutuntersuchung vorzunehmen, u. bei der er überraschender Weise Malariaplasmodien im Blut findet. Dasselbe gilt auch für Kinder, die mit scheinbar eindeutigen Krankheitssymptomen wie Angina oder Dyspepsie u. a. zum Arzt kommen. Wenn man, wie dies in Malaria-gebieten der Fall sein sollte, bei jedem Patienten grundsätzlich eine Blutuntersuchung anstellt, so ist man über die Häufigkeit des Vorkommens der okulten Malaria erstaunt.

2) *Die angeborene Malaria.* Ihr Vorhandensein wird auch

heute noch trotz einwandsfreier Beobachtungen in der Literatur von manchen Autoren abgelehnt. Es seien hier nur die Beobachtungen von JEAN u. VAN NILSON erwähnt, die bei 8 totgeborenen oder kurz nach der Entbindung gestorbenen Neugeborenen 6 mal Plasmodien in der Milz feststellen konnten. Auch die Untersuchungen von BLACKLOCK and GORDON, die bei abgestorbenen Föten in 36 % der Fälle Tropicaplasmodien in der Placenta fanden, sind hier zu erwähnen. In der Literatur finden sich spärliche Einzelbeobachtungen, die aber in überzeugender Weise den Nachweis der angeborenen Malaria erbringen konnten. Ich selbst habe bisher über die wohl grösste Anzahl von Fällen (18) mit angeborener Malaria berichtet, was wahrscheinlich mit den besonders günstigen Bedingungen meiner klinischen Beobachtung zusammenhängen dürfte. Die Schwierigkeiten der Diagnose der angeborenen Malaria dürften hauptsächlich darin liegen, dass der Verlauf der Neugeborenen- u. auch späterhin der Säuglingsmalaria vielfach ein okulter ist. Die nicht selten erhobenen Einwände gegen die Diagnose der angeborenen Malaria, die sich vor allem auf die Annahme einer »normierten Inkubation« stützen u. als Kriterium den Nachweis der Malariaplasmodien entweder im Nabelschnur- oder Placentablut bzw. im Blut des Neugeborenen während der ersten Lebenstage fordern, sind abzulehnen, da bei der Malaria keine »normierte Inkubation« besteht, vielmehr die Inkubation bei natürlicher Infektion zwischen 8—30 Tagen liegt, darüber hinaus die »verzögerte Inkubation« über Monate, selbst Jahre hinaus (»lange Latenz«) die Manifestationen der Malaria verzögern kann.

Bei den besonderen Bedingungen der Übertragung der Malaria von der Mutter auf das Kind in utero wird die Massivität der Infektion grossen Schwankungen unterliegen, was die Inkubationsperiode weitgehend beeinflussen dürfte. Dazu kommt die besondere Disposition der Neugeborenen u. Säuglinge zu dem okulten Verlauf der Malaria. Es ist so durchaus verständlich, dass die Manifestationen der angeborenen Malaria gelegentlich früh, häufig aber erst nach einer »langen Latenz« zum Ausbruch kommen. Endlich kommt noch hinzu, dass die Malaria, auch wenn sie schon früh eindeutige klinische Erscheinungen zeigt,

nicht selten erst spät diagnostiziert wird, da eine gewisse Kenntnis der Symptome der okulten Malaria dem Arzte geläufig sein müssen.

Das zeitliche Auftreten u. das Ausmass der klinischen Manifestationen der angeborenen Malaria hängt von folgenden Faktoren ab:

1) Termin der Infektion des Kindes im Zusammenhang mit einem Malaria-Anfall der Mutter während der Gravidität bzw. dem Geburtsvorgang.

2) Massivität der Infektion.

3) Pathogenität der Malariaplasmodien sowie der Plasmodienarten.

4) Reaktionsbereitschaft des kindlichen Organismus.

5) Altersbedingten konstitutionellen Besonderheiten, die ganz allgemein den Ablauf der Malaria beeinflussen.

6) Die Inkubationsperiode der Malaria ist nicht normiert u. darf daher für die Diagnose der angeborenen oder post partum erworbenen Malaria nicht bewertet werden.

In bisher nicht veröffentlichten Beobachtungen aus einem Säuglingsheim in Ankara wurden während der Winter- u. Spätherbstmonate, in denen eine frische Infektion durch *Anopheles* aus klimatischen Gründen (Durchschnittstemperatur unter 15° Celsius) ausgeschlossen ist, 10 weitere Fälle von sicher angeborener Malaria festgestellt (Ausführliche Veröffentlichung in den *Annales Paediatrici*). Eine derartige Häufung von Fällen mit angeborener Malaria an einer örtlich u. klimatisch fixierten Stelle weist darauf hin, dass die angeborene Malaria keineswegs selten ist. Solche Untersuchungen sind nur möglich an Orten, in denen die Malaria saisongebunden auftritt.

Als Kriterium für die Diagnose der angeborenen Malaria sind folgende Punkte von Bedeutung:

A) Bestehen einer Malaria-Erkrankung der Mutter bzw. eines Malaria-Anfalls während der Schwangerschaft, besonders im letzten Schwangerschaftsmonat oder unmittelbar vor oder während der Entbindung. Nach Möglichkeit soll die Plasmodienart bei Mutter u. Kind festgestellt werden, die natürlich übereinstimmen muss.

B) Nachweis der Plasmodien im Blut der Neugeborenen oder Säuglinge jenseits der Neugeborenenperiode, gleichzeitig Nachweis anderer Malaria-symptome einschliesslich der Syndrome der für diese Altersklasse so charakteristischen Verlaufsform der okulten Malaria, deren genaue Kenntnis vorausgesetzt werden muss.

C) Die Entbindung u. der Aufenthalt (Pflegebedingungen) des Neugeborenen oder Säuglings jenseits der Neugeborenenperiode muss unter Umständen erfolgen, die eine postnatale Infektion als ausgeschlossen erscheinen lassen. Dies ist vor allem an Orten möglich, wo die Malaria nur saisongebunden auftritt.

Falls die Punkte A), B) u. C) bei demselben Fall übereinstimmen, ist man berechtigt, die Diagnose der angeborenen Malaria zu stellen. Dies gilt auch für den idealen, aber in der Praxis aus äusseren Gründen wohl nur selten zutreffenden Fall bei dem

D) der Nachweis der Plasmodien im Nabel- bzw. Placentalblut gelingt.

Die Besonderheiten der Säuglingsmalaria u. der Malaria der Kleinkinder bestehen darin, dass die Malaria in dieser Altersperiode besonders wenig »Lehrbuchmässig« verläuft, d. h. unter dem Bilde der okulten Malaria sich häufig abspielt. Die Fieberreaktionen sind häufig gering, selbst wenn man im Blutbild zahlreiche Plasmodien findet. Daneben gibt es aber auch Säuglingsmalaria mit stürmischen Fieberreaktionen. Eine dem Kinderarzt in Malariagebieten geläufige Form der Malaria dieses Alters ist die *Malaria-Dyspepsie* bzw. *Enteritis*, bei der die Plasmodien im Blut die Diagnose sichern u. bei der die Durchfallserscheinungen schlagartig auf Chinin- oder Atebrinbehandlung aufhören, während alle anderen Behandlungsmethoden einschliesslich Diät oder Sulfonamidbehandlung ergebnislos bleiben. Es handelt sich also dabei um eine für diese Altersperiode sehr charakteristische »*intestinal Form der Malaria*«.

Eine weitere besondere Form der Malaria dieses Alters ist die unter dem Bilde der Säuglingstoxikose verlaufende »*Malariatoxikose*«, das ein Malariacoma darstellt, dabei aber in allen Einzelheiten dem Symptomenbild der Säuglingstoxikose entspricht. Die rechtzeitige Diagnose durch den Plasmodiennachweis im

Blut ist lebensrettend, da eine antimalarielle Behandlung rasch die Erscheinungen zurückgehen lässt.

Die *Dystrophie der Säuglinge u. Kleinkinder* mit allen Abstufungen bis zur Dekomposition als Folge der Malaria (*»Malaria-Dystrophie«*) kommt verhältnismässig häufig bei chronischer, meist okulter Malaria in den Malariagebieten vor. Die Milz ist dabei häufig nur wenig vergrössert, auch bei langer Dauer der Malaria, ein Hinweis auf die mangelhafte Reaktionsbereitschaft des reticulo-endothelialen Gewebes.

Die *Malaria der älteren Kinder* zeigt neben dem bekannten »lehrbuchmässigen« Verlauf nicht selten auch das Bild der okulten Malaria. Eine besondere Form dieser Altersklasse ist die *»typhöse Form der Malaria«* (*»Malariatyphoid«*), die das klinische Bild des Typhus abdominalis weitgehend kopiert (Delirien, Durchfälle, Verstopfung, trockene Zunge, Leber- u. Milzschwellung, positive Diazoreaktion, Leukopenie) und die nur durch den Nachweis der Plasmodien im Blut differentialdiagnostisch zu unterscheiden ist. Sie stellt eine Sonderform des Malariacomas vor.

Auch der *gastrische Symptomenkomplex bei Malaria* als Folge einer plötzlichen Milzschwellung im Malaria-Anfall soll hier erwähnt werden, da er gelegentlich zu diagnostischen Irrtümern führt (Gastralgien, Pseudo-Appendicitis, Pseudo-Peritonitis).

Die *chronische Malaria* ist in den endemischen Malariagebieten bei Kindern nicht selten u. der Milzindex als Masstab der Malariaverseuchung kann in manchen Gebieten 100 % betragen. Eine besondere u. leider nicht seltene Komplikation dieser Form ist die *Lebercirrhose*. Es ist noch heute nicht klar, welche Faktoren massgebend dafür sind, dass der eine Malariakranke eine Cirrhose mit wechselnd grossem Milztumor u. Lebervergrösserung sowie Ascites entwickelt, während andere Kinder mit chronischer Malaria davon verschont bleiben. Möglicherweise hängt dies mit den individuell verschieden verlaufenden Selbstimmunisierungsprozessen bei der Abwehrreaktion des Organismus zusammen, bei denen es unter bestimmten uns noch unbekannten Bedingungen zu einer sich überstürzenden Reaktion im endothelialen-reticulären Gewebe kommt u. im weiteren Verlauf zu der Hyper-

trophie von Milz bzw. Milz u. Leber mit ihren weiteren zum Tode führenden Auswirkungen auf den Kranken.

Eine weitere Komplikation sind die »Malaria-Nephrosen«, besonders im Verlauf der Quartana, aber nach meinen Beobachtungen auch bei Teriana u. Tropica. Bei spezifischer Malaria-behandlung heilen sie rasch ab.

Die wichtigsten u. in ihrer Auswirkung das Leben der Kinder am stärksten bedrohenden Komplikationen der Malaria sind diejenigen des *Zentralnervensystems*. Unter ihnen gibt es aber auch solche, die das Leben nicht bedrohen, sondern nur das Allgemeinbefinden beeinträchtigen. Ich habe in meiner Monographie über »Malaria im Kindesalter« diese Komplikationen besonders ausführlich beschrieben u. begnüge mich daher hier, das von mir aufgestellte *Schema der nervösen Komplikationen der Malaria* mitzuteilen.

A) *Coma Prodromalstadium.*

- 1) Cephalgische Form (ausschliesslich Kopfschmerzen).
- 2) Allgemeine Müdigkeit, Unlust, Krankheitsgefühl, Übelkeit, meist gleichzeitig auch Kopfschmerzen, Hypersensibilität u. Hyperaesthesie sowie Erbrechen.

B) *Coma.*

- 3) Coma mit schleichendem Beginn.
- 4) Foudroyantes Coma (scheinbarer »Sonnenstich« bzw. »Apoplexie«).
- 5) Meningitische Form (einschliesslich Ophthalmoplegien).
- 6) Encephalo-Meningitische Form.
- 7) Malaria-toxikose der Säuglinge.
- 8) Typhöse Form (»Malariatyphoid«).
- 9) Epileptische Form (Konvulsionen) mit epilepsieähnlichem Beginn u. Übergang in Coma.
- 10) Tetanische Form.

C) *Schädigungen mit subakutem Verlauf.*

- 11) Neuritische Form.
- 12) Hemiplegische Form.
- 13) Athetotische Form.
- 14) Ambliopie.

- 15) Ophtalmoplegie (siehe auch B) 5).
- 16) Neuropathische Form.
- 17) Psychosen.

Die im Abschnitt C) zusammengefassten Formen verlaufen meist als okulte Malaria u. erst der manchmal nur zufällig erhobene Blutbefund weist auf die Ursache dieser nervösen Störungen hin, die auf eine spezifische Behandlung hin meist rasch verschwinden.

Was die *Behandlung der Malaria* im Kindesalter anbelangt, so handelt es sich dabei im Prinzip um dieselben Heilmittel wie bei den Erwachsenen. Der Unterschied betrifft nur die Frage der Dosierung, die im Kindesalter relativ hoch ist. Auch Neugeborene u. junge Säuglinge vertragen im allgemeinen sowohl Chinin wie Atebrin bzw. Plasmochin. Schädigungen durch jedes dieser Heilmittel werden gelegentlich in jeder Altersgruppe beobachtet. Bei Kindern wird man sich verhältnismässig häufiger zu Injektionen der Arzneimittel entschliessen müssen. (Widerstand gegen die bitter schmeckenden Heilmittel, Erbrechen, Durchfälle mit herabgesetzter Resorption).

In den endemischen Malariagebieten ist im allgemeinen die *Malariaphylaxe* mit Arzneimitteln über längere Zeit nicht erfolgreich durchzuführen. Auch die Sanierung der Wohnung (D. D. T., Flit, Moskitonetz, Drahtfenster) ist schon mit Rücksicht auf die Lebensgewohnheiten u. die Beschaffenheit der Wohnungen im allgemeinen nicht sehr erfolgversprechend. Nur die systematische Sanierung der näheren u. weiteren Umgebung der Wohnungen (Trockenlegung der Brutstätten der Malariaüberträger (Anopheles) u. die Schaffung hygienischer Wohnstätten, verbunden mit einer Hebung des Lebensstandarts ist wirklich erfolgreich im Kampf gegen die Malaria. Wir Kinderärzte sollten ausserdem noch unsere Aufmerksamkeit auf die Sanierung der Gametenträger (akut u. vor allem chronisch Malariakranke) in der Umgebung der Kinder lenken (Plasmochinbehandlung), wobei manche Übertragung auf Kinder verhütet werden kann. Endlich ist es unsere Pflicht, auf die Notwendigkeit der Malariabehandlung u. Malariaphylaxe während der Gravidität hinzuweisen.

Section 6—Rheumatic Fever.

La fièvre rhumatismale dans ses rapports avec les autres fièvres de nature allergique.

Par **Paul Giraud, René Bernard et Rounel**, Marseille, France.

Avant d'aborder l'étude des différentes manifestations cliniques susceptibles de déclancher une fièvre dite allergique, il nous paraît indispensable de donner une idée précise de ce que nous entendons sous ce vocable.

1°) La fièvre dans ses rapports avec les manifestations allergiques.

Après une première agression d'un antigène quelconque, l'organisme se trouve vis à vis de celui-ci dans un état différent d'un organisme neuf; on dit qu'il est sensibilisé à cet antigène.

Cette sensibilisation, ce souvenir organique, a un double substratum: humoral d'un part, tissulaire d'autre part.

Humoral: Ce sont les anticorps circulants responsables de l'anaphylaxie. D'où la transmission possible de celle-ci d'un individu à l'autre.

Tissulaire: Ce sont les anticorps sessiles élaborés dans les cellules du vaste réseau réticulo-endothélial qui deviennent ainsi le substratum de la mémoire tissulaire. C'est donc lui qui serait responsable des phénomènes allergiques.

Comment concevoir le mécanisme intime de cette allergie?

Lors d'une agression itérative d'un antigène quelconque (chimique ou microbien) les cellules réticulo-endothéliales seront le siège d'un conflit (antigène-anticorps sessiles). Ce conflit aura deux conséquences:

Une d'ordre chimique: décharge d'histamine qui passera dans le sang et déclanchera les phénomènes vaso-moteurs ou cutanéo-muqueux que l'on sait.

l'autre d'ordre végétatif. On connaît depuis Reilly les étroites connexions qui unissent le mésenchyme actif et le système nerveux autonome. Ces inter-réactions sont à double sens. Et si les excitations du sympathique entraînent des modifications profondes des cellules réticulo-endothéliales, inversement, il est possible d'admettre que les bouleversements cellulaires provoqués par la réaction anticorps-antigènes, ébranlent à leur tour le végétatif dont elles dépendent. Cet ébranlement végétatif variable avec chaque sujet et chaque antigène, atteindra les centres di-encéphaliques diffusant ainsi à tout l'organisme. Ainsi s'expliquent les différentes manifestations cliniques allergiques et parmi elles, la fièvre.

En effet, si la pathogénie de la fièvre est encore assez mal élucidée, on admet généralement qu'elle peut avoir à son origine deux mécanismes essentiels:

- a) action directe des toxines ou microbes sur le centre thermorégulateur di-encéphalique.
- b) action indirecte sur ce centre des ébranlements du sympathique périphérique.

C'est de ce second mécanisme que dépendent à notre avis, les fièvres allergiques, objet de notre communication.

2°) Les critères cliniques, biologiques et thérapeutiques des fièvres dites allergiques.

A) Critères cliniques.

Nous distinguerons, d'une part, la courbe thermique et les signes généraux qui l'accompagnent, d'autre part, les manifestations associées variables avec la nature même de l'allergène.

1) *La température* peut revêtir tous les types, mais elle affecte le plus souvent une allure régulière, en plateau ou à faibles oscillations. Elle peut atteindre des chiffres très élevés et sa durée est éminemment variable, souvent très longue en cas d'abstention thérapeutique.

A cette intensité des manifestations fébriles s'oppose presque toujours la pauvreté des autres signes généraux: le pouls est rapide, mais l'état général est souvent excellent, le tuphos exceptionnel et l'appétit lui-même peut être conservé.

2) *Les manifestations associées* par contre présentent des aspects très divers, et nous ne pouvons ici qu'en ébaucher les éléments fondamentaux:

a) *Manifestations cutané-muqueuses.* C'est dans ce cadre qu'il faut placer les éruptions urticariennes, les érythèmes marginés, érythèmes polymorphes, érythèmes noueux, voire même les nodules de Meynet. Certaines angines peuvent être également placées dans ce groupe.

b) *Manifestations viscérales.* Elles sont innombrables mais toutes sous la dépendance des réactions congestives ou cellulaires du mésenchyme actif:

réactions synoviales, douleurs et gonflements articulaires.

exsudation fibrineuse des séreuses: péricarde, plèvre, péritoine.

manifestations congestives, oedémateuses et hyperplasie tissulaire au niveau du poumon, et des tuniques du coeur.

c) *Hyperplasie du tissu lymphoïde.* Amygdales, rate et ganglions.

B) Critères biologiques.

Ces fièvres allergiques ont une expression peu caractéristique. La numération des globules rouges et blancs et la formule leucocytaire sont à la limite de la normale ou présentent quelquefois une tendance lympho-monocytaire. Le taux de la fibrinémie est souvent augmenté.

Mais c'est surtout la *sédimentation* qui offre ici un intérêt majeur; elle est toujours très fortement accélérée même quand la fièvre est peu élevée et c'est cette courbe de sédimentation des hématies qui sera l'un des meilleurs critères pour la conduite thérapeutique.

C) Critères thérapeutiques.

C'est ici que nous touchons le point essentiel de notre étude. En effet, nous possédons là deux critères qui, à notre avis, permettent à eux-seuls de confirmer la nature allergique d'une fièvre; c'est:

d'une part, l'inefficacité presque totale des antibiotiques utilisés seuls.

d'autre part, l'action remarquable et quasi immédiate dans ces cas de certains médicaments à tropisme végétatif comme le salicy-

late de soude, l'antipyrine, le pyramidon. Ces trois médicaments en effet, d'après les recherches récentes de Danielopolu, Popescu et Crivetz, interviennent dans le fonctionnement du système végétatif en bloquant le sympathique. Ils interrompent ainsi les connexions étroites qui, on l'a vu, relient le tissu réticulo-endothélial et les centres végétatifs. Ainsi serait rompu le cercle vicieux qui est à l'origine de la plupart des manifestations allergiques.

3°) Les fièvres allergiques en dehors du rhumatisme articulaire aigu.

C'est sur ces trois critères cliniques, biologiques et thérapeutiques que nous nous sommes basés pour grouper dans une même étude des manifestations apparemment aussi diverses que:

Les fièvres de primo-infection tuberculeuse.

Certaines manifestations de la période secondaire de la scarlatine que l'on a l'habitude de grouper sous le nom de rhumatisme scarlatin.

Enfin, les accidents sériques tardifs.

A) Les fièvres de primo-infection tuberculeuse.

La nature allergique de cette manifestation si répandue chez l'enfant ne fait plus de doute pour personne. La fièvre peut en être le symptôme unique pendant toute la durée de l'évolution et seules les réactions biologiques et la radiographie permettent souvent d'en déceler l'origine.

Dans d'autres cas, au contraire, elle est associée à des manifestations allergiques telles que: érythème noueux, conjonctivite phlycténulaire, réaction pleurale, pleuro-pulmonaire, voire péritonéale et articulaire (purpura rhumatoïde).

Le critère thérapeutique dont nous avons parlé tout à l'heure s'est avéré ici particulièrement démonstratif. Nous avons pu, en effet, dans plus de quinze observations de primo-infection indiscutable, vérifier l'efficacité remarquable de la médication antiallergique: salicylate de soude et antipyrine données à des doses analogues à celles utilisées dans le rhumatisme articulaire aigu.

En 48 heures, trois jours au maximum, la température redevient normale et, à condition de prolonger suffisamment le

traitement (15 jours à 3 semaines en moyenne) l'apyrexie est définitive. Cette chute thermique s'accompagne d'une amélioration parallèle de l'état général et des manifestations associées, et d'un retour progressif à la normale de la courbe de sédimentation. C'est à cette dernière que nous nous référons pour diminuer progressivement la thérapeutique anti-allergique.

B) Les manifestations allergiques de la période secondaire de la scarlatine.

Cette fièvre éruptive malgré les innombrables travaux et les nombreuses théories auxquels elle a donné lieu, pose encore un problème pathogénique, à la vérité malrésolu.

Certains faits sont cependant actuellement hors de discussion depuis les travaux des frères Dick et Dochez en Amérique, de Nicole, Debré, Reilly, Gastinel et Conte en France:

a) La scarlatine est due à n'en point douter à certaines races de streptocoques, hémolytique en particulier, ainsi que déjà en 1906 l'avaient soutenu Mauser et Bergé.

b) Ces streptocoques possèdent une toxine érythrogène à tropisme végétatif, tropisme qui ne se manifeste que lorsque le germe se développe dans une région riche en innervation sympathique.

c) Cette toxine déclanche dans l'organisme une immunité relativement solide et durable.

d) Mais elle peut aussi sur certains terrains particuliers créer, en même temps, et le fait est admis depuis longtemps pour la tuberculose, un état de sensibilisation de l'organisme, à de nouvelles décharges toxiques.

Ces notions théoriques d'une part, les résultats obtenus grâce à la thérapeutique moderne dans les différentes manifestations de la scarlatine d'autre part, nous permettent de concevoir, au moins provisoirement, le déroulement des faits de la façon suivante.

Pendant l'invasion: prolifération microbienne et sécrétion locale des toxines, expliquent les phénomènes de type infectieux observés à cette période.

Phase éruptive: la pullulation microbienne locale se poursuit.

Le taux des toxines dépasse un certain seuil et, par voie sanguine probablement entraîne un *ébranlement* végétatif généralisé.

D'où, l'éruption caractéristique mais observable dans d'autres ébranlements végétatifs de causes diverses (médicaments en particulier);

d'où la fièvre qui résiste à la médication bactériostatique;

d'où également dans certains cas les arthralgies banales à cette période, le blocage rénal de type nettement vaso-moteur;

et enfin, exceptionnellement, le syndrome malin, point culminant du déséquilibre végétatif.

Cette première flambée, en dehors de certains cas relativement rares de scarlatines graves est souvent de courte durée, l'organisme a jugulé la prolifération microbienne et tout rentre dans l'ordre.

Période secondaire, dite des complications:

Dans certains cas cependant, après une courte accalmie, une deuxième flambée microbienne se produit. Sa localisation est alors variable: elle peut se faire au lieu même de l'angine initiale mais plus souvent au niveau du relai lymphatique cervical; c'est le bubon scarlatineux. Parfois, elle se développe dans les cavités voisines: oreille moyenne, sinus. Enfin, quoique plus rarement, on peut observer des foyers à distance au niveau du rein, du coeur, de la plèvre et du poumon et exceptionnellement une véritable septicémie à streptocoques.

Cette deuxième flambée microbienne va déclencher une deuxième vague d'assaut toxinique sur un organisme déjà sensibilisé. Or, cette sensibilisation, cette mémoire organique, a pour substratum indiscuté le système réticulo-endothélial. Aussi, si la deuxième flambée se produit dans une région riche en tissu réticulo-endothélial, telle que amygdale, ganglion, coeur, poumon, elle déclanchera une série de réactions secondes que l'on groupe en clinique sous le nom de manifestations allergiques.

En somme, les complications de la scarlatine, si l'on admet cette hypothèse, peuvent se classer en deux ordres de manifestations.

Les unes dues à la prolifération streptococcique elle-même, de type franchement infectieux et obéissant de façon spectaculaire aux antibiotiques: sulfamides et pénicilline.

Les autres dues à l'imprégnation toxinique du système réticulo-

endothélial déjà sensibilisé et que nous grouperons dans le cadre des manifestations allergiques.

Nous retrouvons ici la *fièvre* avec ses différentes modalités et sa résistance à la thérapeutique anti-infectieuse,

les *arthralgies* satellites presque constants quoique d'intensité fort variable de tout ébranlement végétatif;

enfin l'atteinte relativement fréquente des tuniques du cœur pour lesquelles le streptocoque a, on le sait, un tropisme tout particulier;

plus rarement la plèvre et le poumon peuvent participer à l'ébranlement, comme nous en avons eu plusieurs exemples personnels.

Les critères biologiques hyperfibrinémie et accélération impressionnante de la sédimentation ne manquent jamais.

Enfin fait d'un intérêt pratique considérable, le critère thérapeutique vient ici confirmer la nature allergique de ces manifestations. Elles obéissent en effet de façon non moins spectaculaire à l'administration de salicylate et d'antipyrine. Il existe cependant des échecs indiscutables de cette thérapeutique: ceux-ci s'expliquent aisément si l'on admet que la manifestation allergique n'est que le témoin d'une infection microbienne localisée mais indiscutable. C'est pourquoi il nous a paru logique dans ces cas d'associer à la thérapeutique anti-allergique la pénicilline à doses massives (il s'agit d'un foyer profond et fauci-microbien).

Cette pratique nous a donné, dans bon nombre de cas, d'excellents résultats.

C) La maladie sérique.

Abandonnant les processus allergiques d'origine toxique nous envisagerons maintenant rapidement l'une des manifestations cliniques les plus répandues de l'allergie chimique: la maladie sérique.

Il est classique d'exclure de son cadre les troubles immédiatement consécutifs à l'administration de serum et qui sont du ressort de l'anaphylaxie. Ils ne s'observent en général que chez des sujets soumis antérieurement à une sérothérapie et constituent un phénomène d'ordre purement humoral.

La maladie sérique, au contraire, individualisée par V. Pirquet apparaît dans la huitaine qui suit l'introduction des albumines animales. Elle fait intervenir à l'opposé de l'anaphylaxie le système réticulo-endothélial et ses anticorps sessiles.

Le conflit entre ces anticorps et les albumines étrangères encore circulantes entraînera les deux conséquences déjà décrites au début de notre exposé:

d'une part, décharge d'histamine avec ses phénomènes vaso-moteurs immédiats: urticaire, prurit, oedèmes.

d'autre part, prolifération réticulo-endothéliale avec ses conséquences locales (arthralgies, adénopathies, splénomégalie, angine) et générales (fièvre de type allergique, mononucléose, accélération de la sédimentation sanguine).

Ces divers accidents sont en général très fugaces et rétrocedent le plus souvent en 2 ou 3 jours.

Dans certains cas, cependant, ils peuvent se montrer plus tenaces: fièvre et arthropathies surtout. Et l'on a pu décrire de véritables crises de Rhumatisme Articulaire Aigu déclenchées par les accidents sériques.

Dans les formes passagères où prédominent les manifestations de type histaminique, les antihistaminiques de synthèse suffiront à juguler les symptômes les plus désagréables. Dans les formes prolongées au contraire, de type pseudo-rhumatismal le salicylate et l'antipyrine nous ont toujours donné d'excellents résultats témoignant une fois de plus de leur spécificité anti-allergique.

4°) Les rapports des autres fièvres allergiques avec la fièvre rhumatismale.

1) Analogies entre le R. A. A. et les autres syndromes allergiques.

Il nous paraît inutile d'insister longuement sur les analogies étroites qui existent entre les manifestations du R. A. A. et celles de certains processus allergiques que nous venons de décrire. En particulier, les ressemblances du R. A. A. avec le rhumatisme scarlatin sont telles que de nombreux auteurs on pu parler d'identité (Grenet, Gallacardin, Blechmann). Nous retrouvons ici les principaux critères cliniques, biologiques et thérapeutiques déjà

mentionnés. Les altérations anatomiques décrites comme spécifiques de cette affection se retrouvent elles aussi dans d'autres processus allergiques d'étiologie variée.

L'expérimentation enfin, grâce aux travaux de Kling, Bieling, Besançon et Delarue, a démontré la possibilité de réaliser des formations pathologiques absolument analogues au nodule d'Aschoff, chez des animaux sensibilisés aux toxines les plus diverses, voire à de simples protéines.

2) Discussion sur l'autonomie du R. A. A.

Aussi certains auteurs ont-ils pu nier l'autonomie du R. A. A. en tant que maladie et en faire une simple réaction hyper-allergique aux infections les plus diverses (Mirsky).

Il semble cependant que si le B. K., la fièvre typhoïde, voire même les traumatismes et les injections de serum ont pu être rendus responsables de la Maladie de Bouillaud, celle-ci peut être considérée dans la majorité des cas comme due à certaines races de streptocoques: Vindaus hémolytique en particulier.

Nous ne croyons pas possible d'isoler le Rhumatisme scarlatin du R. A. A. car ces deux affections ont une symptomatologie et une évolution absolument identiques.

3) La part de l'infection et de l'allergie dans le R. A. A.

Mais peut-être faudrait-il à la lumière de cette étude sur les différentes manifestations de l'allergie tissulaire reconsidérer la part qui revient dans le Rhumatisme de Bouillaud, aux germes d'une part, aux réactions du terrain d'autre part.

On ne peut nier comme le faisait remarquer Weil et plus récemment encore Bezançon, que la part du terrain est ici prépondérante. Mais les recherches bactériologiques modernes, de Cecil, Anna K. Hau, Collis et Green ont démontré la présence de streptocoques dans le sang, dans les ganglions, dans le coeur même des rhumatisants avec une grande fréquence. D'autre part, il existe de nombreuses formes de passage entre l'endocardite maligne à forme lente et le rhumatisme cardiaque isolé, comme l'ont bien souligné Olmer et ses collaborateurs.

Il semble donc en définitive qu'il y ait place dans la pathogénie

pour le R. A. A. pour les deux ordres de processus: infectieux et allergique.

a) Lorsque le processus allergique est au premier plan et qu'il obéit immédiatement à la médication salicylée on parle de R. A. A.

b) Lorsque, au contraire, l'infection domine la scène, et que la preuve bactériologique de son existence peut être faite aisément on parle d'endocardite lente. La pénicillinothérapie par son efficacité vient confirmer le diagnostic.

c) Mais il est de nombreux cas limités où la thérapeutique salicylée échoue et où pourtant l'existence d'une bactériémie ne peut être mise en évidence.

Du reste la pénicillinothérapie isolée se montre tout aussi inefficace. On parle alors de Rhumatisme cardiaque évolutif.

Peut-être ne s'agit-il dans ces cas que de la juxtaposition de deux ordres de phénomènes:

Infection d'un part.

Réaction allergique violente entretenue par cette infection d'autre part.

4) Conséquences thérapeutiques.

Les résultats thérapeutiques que nous avons obtenus dans certains cas de rhumatisme scarlatin et de maladie de Bouillaud résistant à la thérapeutique habituelle, semblent confirmer cette hypothèse. En effet, là où la médication anti-allergique seule avait échoué, tout comme la médication anti-infectieuse isolée, l'association pénicilline à doses massives plus salicylate ou antipyrine nous a donné des résultats inespérés. Des constatations analogues ont été faites par Mattéi et ses collaborateurs chez l'adulte.

Ainsi donc de cette étude sur les fièvres de nature allergique peuvent se dégager deux notions essentielles:

L'une de pathologie générale. C'est l'existence chaque jour plus évidente d'une *spécificité réactionnelle* avec ses critères cliniques, biologiques et thérapeutiques, à côté de la *spécificité microbienne*.

L'autre d'ordre pratique: c'est l'utilisation logique et efficace de la médication anti-allergique au cours des processus les plus divers et de l'intérêt que présente, dans certains cas particuliers, son association aux antibiotiques à doses massives.

Observation 1. Le Jeune Robert Ga . . . , 6 ans, est hospitalisé pour érythème noueux. Trois semaines auparavant, otite gauche traitée par sulfamides (10 grs en trois jours), puis paracétésée. Quinze jours plus tard, otalgies droites et pointe de congestion pulmonaire droite avec fièvre à 38°—39°. Nouvelle sulfamidothérapie: cinq grammes en tout, dont l'inefficacité entraîne l'admission.

A l'examen, assez bon état général, fièvre persistante à 38°8, sur les jambes érythème contusifforme. La tache érythémateuse est surélevée et disparaît à la pression. Par ailleurs, excepté une rate perceptible sur deux travers de doigt, l'examen est négatif.

Antécédents nuls. Un certain nombre d'examens complémentaires sont pratiqués:

O. R. L.: rien d'anormal.

Cuti-réaction: très fortement positive.

Temps de sédimentation des hématies: très accéléré, 53 mm en 1 heure, 78 mm en 2 heures.

Radiographie thoracique: image de primo-infection dans la région hilare droite.

Une thérapeutique salicylée est instituée: six grammes per os et par jour. En 24 heures, chute de la température à 37° qui restera ultérieurement normale. Reprise de l'état général avec augmentation de poids. Le salicylate est continué dix jours à doses régressives et l'enfant sort alors apparemment guéri.

L'action du médicament est ici spectaculaire en ce qui concerne la fièvre. Elle est également incontestable sur l'état général ainsi qu'en témoignent la reprise du poids et l'amélioration rapide. L'administration antérieure de sulfamides ne peut être retenue dans la genèse de l'érythème noueux, en effet le contexte clinique, la cuti et la radio ne permettent pas d'hésitation de diagnostic.

Observation 2. L'enfant Jamg . . . , 14 ans, est admis pour érythème noueux. Début quelques jours auparavant par lassitude, fièvre, elles-mêmes précédées depuis un mois par de l'amaigrissement.

A l'examen, malade très asthénique, pouls à 100, fièvre à 39°. Sur les jambes on note une dizaine de nouures contusifformes, chaudes, non douloureuses. Le reste de l'examen est négatif. La cuti-réaction est très positive, une radiographie thoracique montre une opacité importante dans la région hilare droite témoin d'une primo-infection. Numération et formule sanguines normales. Temps de sédimentation des hématies accéléré: 35 mm en 1 heure, 70 mm en 2 heures.

L'antipyrine est administrée à la dose de 6 grs per os et par jour. En 24 heures la température passe de 39°4 à 36°9, niveau où elle va dès lors se maintenir. En même temps, s'améliore visiblement l'état général de l'enfant.

Durant seize jours, l'antipyrine est continuée à doses décroissantes et l'enfant sort, à ce moment l'éruption noueuse ayant totalement disparu.

Un mois plus tard, nouvelle hospitalisation pour un autre épisode fébrile. Au nouvel examen, signe d'épanchement pleural droit avec confirmation radiologique. Le liquide pleural sérofibrineux, a un Rivalta positif, et une lymphocytose élevée; pas de bacille de Koch à l'examen direct. La cuti est toujours positive, la sédimentation sanguine toujours très accélérée. La fièvre se maintient à 39°—39°3.

Thérapeutique salicylée cette fois à la dose de quatre grammes: aucun résultat. Cinq jours après, aucune amélioration ne s'étant manifestée la quantité du médicament est portée à six grammes. Dès lors la fièvre diminue et disparaît complètement en trois jours de façon définitive.

L'état général est bon, les signes radiologiques et cliniques s'amendent rapidement. La sédimentation reste toutefois accélérée à la sortie du malade. La salicylothérapie a été continuée pendant quarante jours à doses regressives.

C'est là un bel exemple de l'action efficace de l'antipyrine et du salicylate qui tous deux ont amené une cédation thermique prompte, prélude à une régression rapide des signes cliniques. On peut remarquer en outre que la médication salicylée n'a produit son effet qu'après avoir été portée à un taux suffisant. Enfin l'évolution ultérieure d'une pleurésie semble indiquer, que ces agents thérapeutiques n'ont qu'un effet transitoire sur l'état allergique, qui se manifeste à nouveau dès qu'on suspend leur administration.

Observation 3. Roger Mon . . . , 12 ans, entre à l'hôpital pour épisode pulmonaire aigu. Début huit jours plus tôt, précédé par une période d'asthénie et d'amaigrissement. Dans les antécédents, on note un contact bacillaire (soeur de 27 ans décédée deux mois plus tôt de tuberculose pulmonaire).

A l'examen, état général assez satisfaisant. Fièvre à 39°. La cuti-réaction est fortement positive, la sédimentation très accélérée: 48 mm et 81 mm respectivement en une heure et deux heures.

La radiographie pulmonaire montre une opacité assez irrégulière de deux régions hilaires, un peu en ailes de papillon. La sulfadiazine prescrite à l'entrée (cinq grammes par jour) amène en quatre jours une cédation thermique à 37° transitoire; une nouvelle période fébrile apparaît en effet deux jours plus tard après arrêt des sulfamides. Une semaine durant la fièvre oscille entre 37°7 le matin et 38°4 le soir.

L'antipyrine est alors administrée, per os, à la dose de deux grammes par 24 heures, la température descend à 37° et s'y maintiendra désormais. Bonne reprise de l'état général, la médication est continuée dix jours et l'enfant quitte l'hôpital en parfait état de santé.

Il y a ici opposition frappante entre l'action des sulfamides d'une part et de l'antipyrine d'autre part. Cette dernière a amené un apyrexie rapide conjointement à une amélioration sensible de l'état général alors que la sulfadiazine n'a provoqué qu'une simple défervescence thermique d'ailleurs

transitoire. Son action paraît limitée à l'élément infectieux, vraisemblablement surajouté au processus allergique, que l'antipyrine au contraire, semble neutraliser électivement.

Observation 4. René Sic . . . , 12 ans $\frac{1}{2}$, entré à l'hôpital avec fièvre à 39°, céphalées, constipation. Début quinze jours auparavant par température à 39°5 le soir, diarrhée, anorexie; depuis courbe thermique oscillant entre 38 et 39°, la constipation a succédé à la diarrhée initiale.

Deux ans et demi plus tôt l'enfant a été soigné pour une péritonite bacillaire qui a évolué pendant deux années.

A l'examen, enfant abattu, fosse iliaque gauche gargouillante, obscurité respiratoire à la base droite. Radiographie: cul de sac costo-diaphragmatique droit comblé. Les jours suivants la fièvre se maintient à 39°. La cuti-réaction est positive. Le temps de sédimentation accéléré: 85 mm en une heure, 115 mm en deux heures.

Une hémoculture, un séro-diagnostic, une recherche du bacille de Koch, après tubage gastrique, sont négatifs. Par contre un nouveau cliché radiographique montre un épanchement gauche confirmé à la ponction (liquide sérofibrineux stérile avec grosse lymphocytose).

L'antipyrine est utilisée à la dose de trois grammes par jour et per os. Aucune amélioration ne s'étant manifestée après quatre jours de cette thérapeutique la posologie est portée à six grammes: en 48 heures cédation thermique. Trois semaines durant et à doses régulièrement décroissantes cette médication sera continuée.

L'état général s'améliore. Malgré la persistance des signes cliniques, la radiographie met en évidence un nettoyage progressif de l'hémi-thorax gauche. La courbe de sédimentation revient peu à peu à la normale. En 8 jours elle passe des chiffres de 60 et 90 mm à 47 et 80 mm, respectivement en une heure et deux heures. L'enfant, un mois après son entrée, part dans un préventorium.

Ce cas confirme les précédents et met en relief, une fois de plus, la nécessité de doses suffisantes. Insistons également sur l'intérêt qu'il y a à suivre l'évolution de l'affection par la courbe de sédimentation.

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The Incidence of Rheumatic Fever in Jerusalem and the beginnings of Chemoprophylaxis.

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Rheumatic fever has not aroused the same interest in Palestine among the public and in the medical profession as it has in England and in U. S. A., possibly because the general course of the disease is not so grave here and does not claim so high a number of victims as in those countries.

Some diseases which seem to be influenced by climatic conditions take a milder course in Palestine. Scarlet fever, for instance, although frequent, may appear in such an abortive form as to cause serious diagnostic difficulties and can only be determined in the second stage of the disease.

The same can be said of rickets which, though present in about 55 % of children, leads to deformities only in rare cases.

Rheumatic fever in Palestine takes mostly an insidious course. It occurs however much more frequently than is generally realized and creates therefore serious medical and social problems.

Our studies were limited to Jerusalem and its outskirts. Jerusalem is situated 827 M. above sea level 31° 47' N and 35° 14' E. Not all sources which are needed for investigation of the incidence of Rheumatic fever were at our disposal. No compulsory notification of Rheumatic fever exists in Palestine and for religious reasons post mortem examinations are seldom possible. Owing to the shortage of beds available in hospitals, especially for chronic diseases, the hospital admission rate could not be considered reliable evidence of the incidence of the disease. We had recourse instead to the local schools where valuable information was to be obtained in line with the researches of Glover, Griffith and John Paul.

The Arab schools in Palestine are under the supervision of the Government Health Department and The Jewish of that of the Department of School Hygiene of the Hadassa Medical Organization, to whose kind cooperation we owe our material. Children suspected or found to be suffering from heart disease by school physicians, were referred to the heart and rheumatic clinic at the Bikur Cholim Hospital. Besides routine clinical examination, blood pictures, sedimentation rate, Electrocardiogram and X-rays, vital capacity and standardized exercise tolerance test were made. Active cases were admitted to the Children's Department of the Bikur Cholim Hospital where beds were assigned for a long stay, and where the patients remained until the complete disappearance of the acute rheumatic manifestations. Normal temperature, sedimentation rate, Weltman reaction and normal electrocardiogram were considered signs of recovery. Hospital treatment lasted several weeks, and, in grave cases several months. After discharge from hospital the cases were referred to the Heart clinic for systematic control and prophylactic treatment.

The diagnosis of rheumatic fever was not always easy. Particularly noteworthy is the extremely rare occurrence of Ashoff nodes and of the typical acute polyarthritis while subacute and subclinical cases with insidious course which nevertheless may cause serious heart-complications are most frequent. The history of such cases has often nothing characteristic: lassitude, perspi-

ration, nosebleeding, abdominal pain, and occasional fever were the only symptoms. The diagnosis is made mostly by the appearance of cardiac involvement and increased sedimentation rate. The interpretation of a systolic murmur may cause diagnostic difficulties, when it has to be decided whether it is a functional murmur, a congenital defect, or a rheumatic valvular defect. Great mistakes can only be avoided by critical and careful consideration of the case history and of all etiological and clinical factors.

The therapy consisted of sodium salicylate, in doses which were able to maintain a blood level of 30—40 mg %. The intravenous method was not used. In some cases which did not respond satisfactorily to salicylates, pyramidon was given with good and prompt results. The grave complication of agranulocytosis never featured in our cases. The treatment was continued until temperature, leucocytecount and sedimentation rate became normal. Then sulfa-prophylaxis was started.

As far as tonsilectomy is concerned every case was dealt with individually and only tonsils with chronic inflammation causing exacerbations were removed. Among our cases there were three in which the first attacks of rheumatic fever occurred 2 or 3 years after tonsilectomy. Another proof that tonsilectomy cannot be considered as a safeguard against rheumatic fever. When the active stage was over the patient was permitted to get up, for a gradually increasing time and later referred for rehabilitation exercises. The results of rehabilitation were most encouraging. Some cases of rheumatic fever showing on admission to hospital signs of grave heart failure and which after recovery were submitted to systematic and carefully graded exercise showed improvement that could hardly have been believed possible. I remember a case admitted in a state of cardiac breakdown with infarction of the lung, enlarged liver and dyspnea which improved to such a degree as to enable the patient to proceed to school by bicycle.

In its 2 years of existence 167 children were referred to and examined in the heart clinic. Of these 124 had organic heart disease while 43 suffered from functional disturbances. Among

the 124 children aged from 4 to 14, 56 were boys, 68 girls, and according to their parentage and origin:

- 61 Ashkenasi (or hailing from Central and Eastern Europe)
- 19 Persian
- 17 Spanish
- 18 Iraque and Kourdistan
- 5 Syrian
- 4 Jemenites.

124

of the 124 cases, 24 had congenital heart defects.

2 were cured cases of subacute bacterial
Endocarditis.

and 98 were rheumatic cases.

As to the illnesses proceding the cardiac legions of rheumatic
origin:

18 were scarlet fever

12 tonsilitis

33 repeated infections of upper respiratory
tract,

8 typical polyarthritis

and in 27 though there was no rheumatic fever his-
tory they showed typical mitral involve-
ment of the heart.

It was often difficult to establish from case history the time of the first attack of rheumatic fever, but in those cases which were under observation from the beginning the age was mostly between 6 and 7, an age incidence somewhat higher than that given by May Wilson.

Chorea deserves special mention. It is according to the accepted conception a manifestation of rheumatic fever, a conception supported by statistics of Finlay and Gibson, which show that 50 to 56 % of Chorea were accompanied by symptoms of Rheumatic fever. In our 26 chorea cases, among which some were grave only 6 had carditis or other manifestations of rheumatic fever. The scarcity of cardiac involvement and of other Rheumatic fever symptoms in our cases, the absence of Ashoffs nodes in

chorea in general, as well as the lack of increased sedimentation rate and leucocytosis makes us doubt the rheumatic origin in all chorea cases. One is rather led to suppose that chorea is not a disease caused by one definite agent but a complex of symptoms which may be caused in some cases by rheumatic fever and in some by other agents which attack in a similar way and result in similar clinical manifestations. Doubts as to the interrelationship of chorea and of rheumatic fever were expressed by Johns & Bland, Coburn and Moore.

The department of school Hygiene of the Hadassa Medical Organization published in its annual reports the following data on organic heart defects among Jewish children. It reads:

Per 100 school children:

	Jerusalem	Tel-Aviv	Haifa	Others	Kinder- gardens	Elementary Schools	Religious Schools
1941	1.5	—	0.8	1.0	0.2	0.9	0.6
1942—44	1.5	1.0	0.7	1.0	0.5	1.0	0.6

Jerusalem takes the first place in frequency. The tremendous influence of social and living conditions and of climate on the epidemiologie of rheumatic fever are generally known. The comparative studies by Glover, Griffith in England and by Paul in the U. S. A. on the subject of the incidence of heart defects among poor and well-to-do people are classical. Rheumatic fever is a poverty disease, although its incidence bears no directly proportional relationship to the degree of poverty.

Of 96 cases investigated by us 84 were of the poor classes of the population. The extensive feeding scheme for school children has contributed greatly to the reducing of undernourishment. But the dwelling conditions among the poorer classes have remained archaic.

Our investigation of the housing conditions of 96 rheumatic patients shows that in 60 % more than 4 persons lived in one room and in 42 % the children had no bed of their own but slept with two or more children.

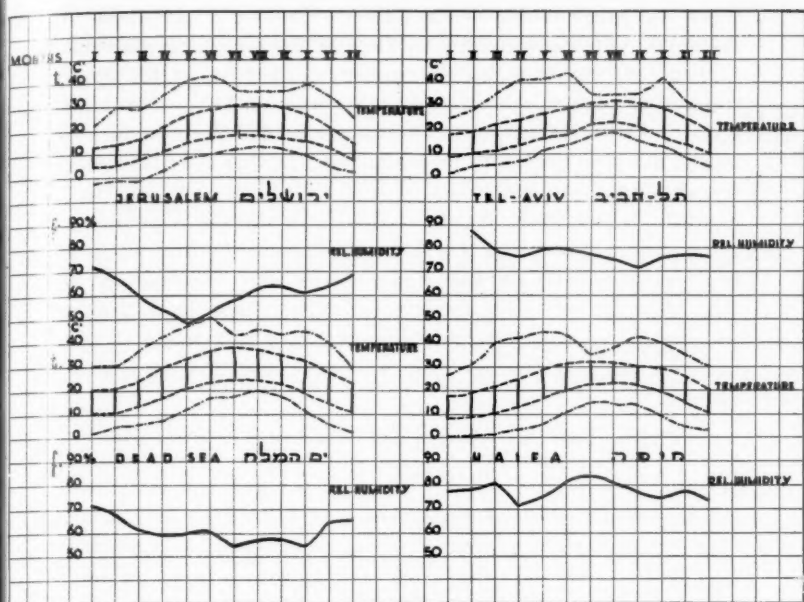
This over-crowding is not limited to the housing conditions,

but exists also in schools in which up to 50—60 children are crammed into one classroom. One must also mention the lack of preliminary sorting and subsequent isolation of infectious cases in the waiting rooms of almost all out-patient clinics in this country.

As to the influence of climatic conditions upon the incidence of Rheumatic fever, we have only to remember the observations of Paul and Dixon among Indian children at the Mexican and Canadian borders which have an almost experimental value and of numerous publications among which those of Holbrook, Coburn, Sterling Nickel, and Maddox are most noteworthy. But what these climatic influences really are is not certain.

Cold and humidity and lack of sunshine have been generally considered to be the main factors predisposing to rheumatic fever. Our observations in Palestine seem not to give direct support to this conception.

Jerusalem has sunshine practically all the year round. The measurements made by Ashbell at the Hebrew University show that there are only seven per cent of totally cloudy days during the year, while 44 % are sunny days and 47 % are sunny and cloudy alternating and that there are 70 % of possible sun radiation hours (3 297 hours of 4 436 possible sun radiation hours). As to cold only in exceptional years does the temperature drop below zero, and during the last 50 years the coldest day was minus 7° C. The mean relative humidity during the year is 60, with a maximum 75 to 80 in January and February and August and September, and a minimum of about 30 in the summer. The fluctuations of humidity during the day in the months of March and April, months of highest incidence of rheumatic fever, are between 60 at night and 45—50 at mid-day. In Jerusalem there is neither cold weather nor dampness nor lack of sunshine. Nevertheless Jerusalem is well known for its climate unfavorably predisposing to infections of the respiratory tract and for the highest frequency of organic heart diseases. One meteorological occurrence seems to be noteworthy and may be suspected to be of importance; this is the daily fluctuations of temperature. In Jerusalem differences between morning and evening tempera-



tures reach 12 to 15° C and in the final stage of sirocco days even as much as 29° C degrees.

One is tempted to infer that these great fluctuations may have damaging effects but still further observations are necessary.

Prophylaxis.

Although the epidemiology and pathogenesis of rheumatic fever is still somewhat obscure, there is one thing certain — namely, that rheumatic fever attacks are always preceded by and follow closely in the wake of streptococcus hemolyticus Lancefield A infections. It was therefore a logical conception to introduce prophylaxis against streptococcus infections as a preventative antirheumatic measure. The experiment made ten years ago by Hansen and Platou with sulfanilamid were followed by many extensive studies in the prevention of rheumatic fever and scarlet

fever and other streptococcus infections among which those of Holbrook, Coburn, and Caroline Thomas deserve special mention.

Our first efforts in the prevention of infections of the upper respiratory tract in rheumatic families began in 1943. Our initial fears as to the toxicity and the danger of sulfafastness in prolonged use soon proved to be groundless. During the first month the children were submitted to weekly control and later to a monthly examination. Where a change in the blood picture or urine or a rash occurred it was usually during the first weeks of the treatment and no disturbing effects were observed by us after the drug was given for a month. The prophylactic dose of sulfadiazine or sulfamerazine at the age of 4 to 6 was a $\frac{1}{4}$ of a tablet or 0.12, at the age from 6—9 0.25, and above 9 years of age 0.5.

If the prophylaxis was interrupted by the patient and then resumed, this resumption did not cause either hypersensitivity or sulfafastness. In dealing with neglected and underprivileged children we experienced oppositions and difficulties only at the start of the regular prophylactic administration. At present it may be said that the value of the prophylaxis is becoming more and more recognized by the public.

Our observations were carried out on 95 patients with 151 patient years, among whom 12 are in the 4th year of treatment. The prophylaxis was continued all the year round and not interrupted in the summer. Of these 95 patients only 2 had rheumatic fever relapses, both of which occurred within the first year of the illness, which is an encouraging result.

This communication does not pretend to convey a complete picture of the rheumatic fever problem in Jerusalem. Our intention is to convey that Palestine with its warm and sunny climate has a rheumatic fever problem which should not be under-rated and which demands study and careful attention. A much longer existence of heart clinics and a more systematic dealing with streptococcus infections would give more definite results. Up till now heart clinics exist only in Jerusalem and Tel-Aviv. The future programme must include the establishment of more heart clinics among the Jewish and Arab population, more careful

studies on the geographical distribution, and more knowledge of streptococcus L. A. infections and their immunological effects on people.

Rheumatic Fever.

By **Wilfrid Sheldon, M. D., F. R. C. P.**

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My first duty is to express my deep appreciation at the invitation to take part in today's discussion of Rheumatic Fever. I would also crave a moment to acknowledge my indebtedness to the late Dr. John Poynton of London, who, by his ceaseless interest in this difficult disease, and his devotion to its victims, fanned the flame of enquiry in so many who were privileged to work with him. His death during the recent war removed from my country a veritable pioneer of acute rheumatism in all its aspects.

I propose to confine my remarks to two aspects of rheumatic fever. I shall first indicate what has been happening to the incidence of the disease in England, and particularly in London; and then discuss some aspects of the prevention of rheumatic fever.

Incidence.

In 1930, at a time when the appalling morbidity caused by the ravages of rheumatic heart disease had roused the Public Health conscience in England sufficiently to set going such measures as rheumatism supervisory centres, and special country hospitals for the care of children with early and potentially recoverable heart disease, Glover made the brave assertion that rheumatic fever was an obsolescent disease. The trend of events since then has tended to support his contention, and it is certainly my impression that the incidence of rheumatic heart disease in London is on the wane. To produce proof of changes in the incidence of a disease which is not notifiable presents, however, obvious difficulties. A reduction in the death rate does not necessarily imply a lowered incidence, particularly if methods of treatment have undergone a radical improvement, as for example the benefit of penicillin in osteomyelitis,

although as far as established rheumatic heart disease is concerned, no dramatic change in treatment can be recorded. Further, a variation in mortality figures, when taken over a long period of years, may owe something to changing medical fashions in ascribing a cause for death.

At the beginning of this century, in England and Wales the crude death rate per million persons from rheumatic fever stood at 67; by 1913, prior to the outbreak of war, it had fallen to 48, and in spite of fluctuations it was still at that level in 1925. During the next fourteen years up to 1939 and the outbreak of the recent war the crude death rate slightly more than halved itself, dropping steadily to 23, but even more remarkable was the sharp drop during the war years, for by 1942 the crude death rate from rheumatic fever had again halved itself to reach 12, the lowest figure on record. Since then the figures have risen slightly, but do not affect the over-all impression of a persistent and striking decline in rheumatic fever mortality.

The Registrar-General's returns for deaths from rheumatic fever do not however necessarily reflect the number of deaths from rheumatic heart disease, for unless rheumatism is specifically mentioned on the certificate of death from heart disease, the death is returned under the heading of heart disease and not rheumatic fever. This difficulty was realised by Glover (1943) and by Gale (1945), and both authors therefore prepared charts comparing the total deaths under 15 years of age from (a) rheumatic fever, and (b) heart disease, to which Gale has also added (c) the total deaths under 15 years due to scarlet fever. Not all the deaths from heart disease under 15 years are due to rheumatic disease, although this is undeniably the commonest cause; Glover estimated that in nine-tenths rheumatic disease was the underlying condition. The outstanding fact is that during the period of enquiry, namely from 1928 to 1944, the total death rate under 15 years from rheumatic fever and from heart disease drop in such closely parallel lines as to remove any doubt of the significance of the decline in rheumatic fever mortality.

Reference has already been made to the difficulty of proving a decline in the incidence, as opposed to the mortality, of rheumatic

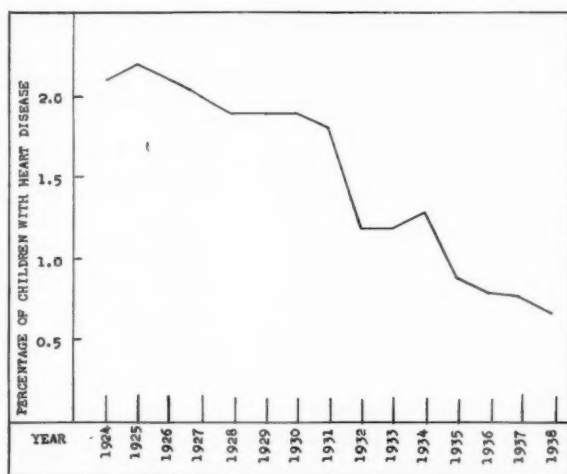


Fig. 1. Percentage annual incidence of heart disease in London elementary school children. (280 000 annual examinations.)

heart disease. Bach's (1939) figures, quoted and extended by Glover (1943), for London elementary school children are shown in Fig. 1. The number of school children undergoing medical inspection annually was about 280 000; the number of children (new cases) found each year to be suffering from heart disease declined steadily from 2.1 per cent in 1924 to 0.68 per cent in 1938, and the graph of these figures falls roughly parallel with that of deaths from heart disease under 15 years.

Two personal experiences may also be cited as evidence. The first concerns the work of the Children's Rheumatism Supervisory Clinic at Walthamstow, a populous and artisan Borough in the East of London. Fig. 2 shows the percentage annually of new cases found to have heart disease, almost entirely due to rheumatism. From 1931 to 1935 roughly 40 per cent of the new cases were found to be thus affected, but from 1935 the percentage steadily dropped, so that by 1939 the figure had halved itself, being 20.3. In the early years of the war, mass evacuation and bombing considerably lowered the attendances, and in order to obtain attend-

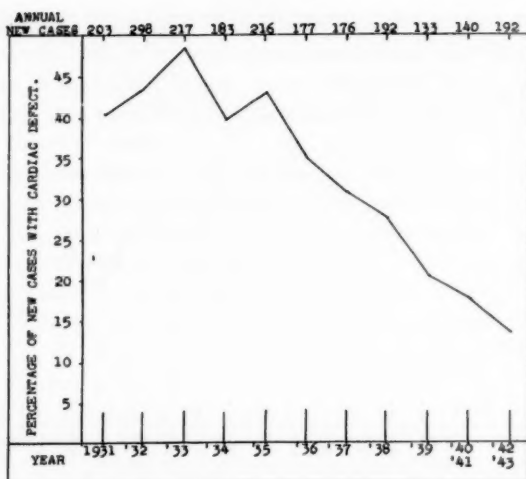


Fig. 2. Walthamstow rheumatism clinic 1931—1943.

ance figures comparable to the pre-war years it will be noticed that the years 1940 and 1941, and 1942 and 1943, have been added together. It is particularly noteworthy that in these years the decline persisted, although the cases were drawn from children whose parents had either refused to accept the offer of evacuation, or had soon recalled their offspring from the rural areas.

The other experience relates to The Hospital for Sick Children, Great Ormond Street. Some twenty years ago from 20 to 25 per cent of the medical beds were constantly filled with children suffering from one or more of the manifestations of acute rheumatism. This figure was falling in the years immediately prior to the war; since the war, the absence of rheumatic children from the wards is as striking as was formerly their abundance. Fig. 3 shows the annual percentage of rheumatic children admitted to the Hospital out of the total admissions, and bears out the above impressions. Although in 1946 the number of beds in the Hospital had not regained the pre-war figure, and owing to the long stay in hospital which rheumatic children require there may be an understandable tendency to seek alternative accommodation for them other than in

PERCENTAGE ADMISSION FOR RHEUMATISM.

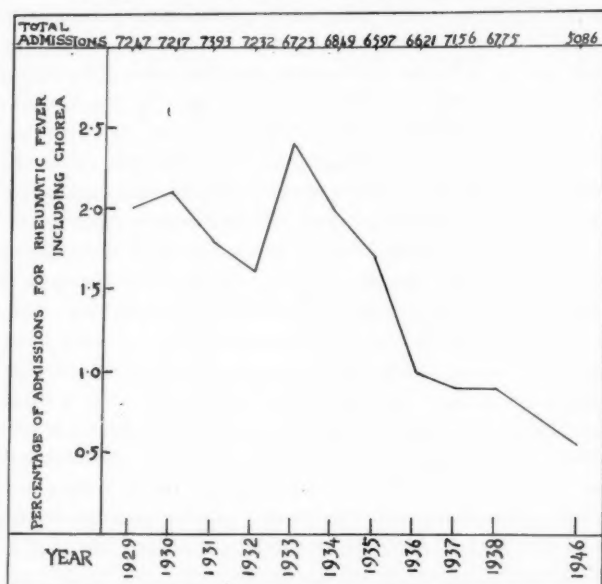


Fig. 3. The Hospital for Sick Children, Great Ormond Street.

a busy general hospital, this will not explain the pre-war decline in the number of cases, nor entirely explain the low figure for 1946. But perhaps a more impressive indication of the decline in rheumatism can be drawn from the hospital's rheumatism supervisory clinic, which before the war was organised in conjunction with the London County Council. The clinic was closed during the war; in 1946 it was decided that the number of rheumatic children now attending the hospital was too small to justify re-opening the clinic.

To summarise: a decline in mortality from rheumatic fever has been proceeding in England throughout this century. A decline in the incidence of acute rheumatic disease among London children was apparent before the war, and the decline accelerated during the war years.

The reasons for these changes offer a field for speculation and research. The lowered mortality during this century has coincided with a gradual rise in the standard of living. The lessening incidence just prior to the war occurred at the same time as a considerable rise in employment. It is tempting to think that the mass evacuation of children from cities and towns into rural areas, which took place at the outbreak of war, may have so reduced overcrowding and the opportunity for droplet infection as to account for the accelerated decrease in rheumatism during the war years. The figures from Walthamstow however show that the decline went on among children who continued to dwell in their own homes, and spent many nights in airraid shelters. On the other hand at two childrens hospitals set up as a wartime measure in rural areas in the County of Sussex, of a total of 4 119 admissions of children of all ages, admissions for acute rheumatic disease including chorea numbered 86 or 2.1 per cent (Cuckfield and Elfinward E. M. S. hospitals). These figures suggest that evacuation to the country was not an important factor. More telling factors may have been full employment with good wages, an equitable distribution of food stuffs due to strict rationing, extra milk for school children, and free school meals.

That the nutritional state of London school children continued to improve during the war is indicated by Mellanby's enquiry into the amount of dental caries (see Fig. 4). A survey in 1929 showed only 4.7 per cent of 5-year old London school children to be free of caries, by 1943 the percentage had risen to 22.4, and by 1945 had risen further to 26.5. There seems some reason to associate the decreasing incidence of rheumatic infection with a diminution of poverty and all that implies in the way of hygiene and nutrition; and if the rheumatic reaction is correctly attributed to a defective

Year	No. children examined	No. teeth examined	% teeth present	% free of caries	% showing severe caries
1929	1 293			4.7	62.8
1943	1 604	36 196	92.2	22.4	29.3
1945	532	13 381	94.4	26.5	

Fig. 4. Condition of teeth in 5-year old London school children.

immunological response against haemolytic streptococcal infection, it may be that an improved standard of living is enabling London children to develop a more normal type of immunity response.

Prevention.

It is convenient to discuss this aspect of rheumatic fever by dividing the illness into the three phases as defined by Coburn in his Rachford lectures (1945). Phase I covers the period of the acute haemolytic streptococcal pharyngitis. Phase II is the ensuing one to three weeks in which the child is afebrile and symptomless. Phase III is the stage of active rheumatic manifestations affecting particularly the heart and joints. There is also what may be called the pre-rheumatic phase, and refers to the period before phase I.

Pre-rheumatic Phase. During this phase the merit of giving rheumatic children a small daily dose of sulphonamide with the object of preventing the pharyngitis of Phase I, and so automatically annihilating phases II and III, has received an extensive trial in America, and there are ample figures to show that by this means the relapse rate in rheumatic children can be much reduced. The method has however certain drawbacks; it involves treating many children who in any case might never develop a relapse; daily drugging must continue for months or years on end; the time to cease treatment is an arbitrary matter, and the benefit conferred during treatment does not persist after treatment is stopped.

If in spite of these objections the method is acceptable, then surely it would be logical to apply it universally to all children during the years when susceptibility to rheumatic fever is known to be highest, in order to cover those children who have not as yet had the opportunity to disclose their rheumatic constitution, in other words, to prevent the first attack of rheumatic fever. In London the number of school children who on any one day may be carrying pathogenic haemolytic streptococci (Lancefield Group A) is roughly 50 000 to 60 000, taking the total number of school children in London to be half a million. As there is at present no means of foretelling the child who may develop a first attack of

rheumatic fever, all children carrying these organisms must be regarded as potential sufferers from rheumatic fever. Fig. 5 shows the results obtained from routine nose and throat swabs of large groups of London school children, reported by the Public Health Department of the London County Council.

	September, 1942			February & March, 1943		
	No. of children	H. S. present	% with H. S.	No. of children	H. S. present	% with H. S.
Under 10 years	548	84	15.3	942	143	15.2
10 years and over.....	648	110	17.0	1106	130	11.7
Total	1196	194	16.2	2048	273	13.3
Type of Organism:						
Lancefield group A		78 %			77.8 %	
" " C		12.5 %			9.1 %	
" " G		0.5 %			0.4 %	
Not grouped		9 %			12.7 %	

Fig. 5. Haemolytic streptococcal carriers among London school children. (Swabs from nose and throat.)

It may well seem that the universal adoption of sulphonamide prophylaxis for all school children would magnify the problem of the rheumatic child beyond its due proportion, and it would be more reasonable to limit its use to children known to be rheumatic, and to regard it as an interim measure until an easier means of prevention can be evolved.

With regard to Phase I, once pharyngitis has developed and been diagnosed, the value of sulphonamide in preventing subsequent rheumatism is negligible. At this stage the mechanism for developing a rheumatic attack has been released, and rapid reduction of the pharyngitis will not inhibit the progress of the rheumatic reaction.

As to Phase III, the use of large doses of salicylate as described by Coburn is clearly promising, and is an approach which must receive further trial and analysis.

There remains Phase II, the period of one to three weeks between the pharyngitis and subsequent acute rheumatism. This

phase would seem to offer the ideal time for prophylaxis, but before it can be used to prevent first attacks of rheumatism, at least two problems await solution. The first is to discover means to identify the child who is utilising this period to set the stage for the ensuing symptoms of rheumatism; the second is to find a reliable means of prophylaxis. Some years have passed since Schlesinger drew attention to the value of aspirin as a prophylactic if given throughout phase II, and I doubt whether this work has received sufficient recognition or had adequate trial. My own experience with aspirin in this phase has left me with a very favourable impression, and in view of Coburn's work with salicylate in Phase III, it may well be that the dosage used in Phase II was insufficient.

Case finding.

Although the early detection of rheumatic heart disease does not strictly amount to prevention, as the illness is already in being, there is no doubt that when early diagnosis is followed by thorough and prolonged rest, there is a prospect of recovery which in many cases may be complete. Early diagnosis is therefore well worth while. It is probable that in England the School Medical Service could play a much more important role in the detection of early cases than is being done at present, when much time is taken up with periodic statutory examinations of school children at definite age groups. Armed with the knowledge that rheumatic heart disease is likely to develop from one to three weeks after a haemolytic streptococcal pharyngitis, the routine inspection of all school children a month after this illness should bring to light those who are starting heart disease, or enable suspected children to undergo expert investigation at a Rheumatism Clinic.

It may be that the advent of a National Medical Service in England will facilitate the introduction of a system by which children who have had a sore throat can be followed up during the ensuing month. When a practitioner has been called to a child with a sore throat, the task of re-examination at the end of a month should either become his duty, or by notifying the school the subsequent examination could be undertaken by the school

medical service. Many children however, do not receive medical attention during the stage of an acute pharyngitis; this difficulty could be overcome if all children who were absent from school for a stated period such as two or more days underwent a medical inspection on their return, and if throat infection was considered the reason for absenteeism, a further examination were to be made one month later. Doubtless such an arrangement would entail skilful administrative planning, and would require a reorientation of outlook regarding the function of the school medical service. It would however make the work of the school medical officer less drab than it is at present, and would enhance the part played by this service in the supervision of the health of school children.

For some years in Walthamstow a follow up system, somewhat on the lines indicated above, has been in operation. Knowing that scarlet fever is a haemolytic streptococcal infection, and that diphtheria may be complicated by infection with this organism, since 1931 the Medical Officer of Health has arranged to examine all children admitted to the local Isolation Hospital on account of these diseases, within a month of their discharge, and to refer to the Rheumatism Clinic those children in whom he suspected the heart to be in any way abnormal. Fig. 6 shows the results of this investigation for the period 1931 to 1939. It will be seen that during these years 131 children who had had scarlet fever were picked out for reference to the Rheumatism Clinic, and that of these 69 were judged to have evidence of cardiac disease. In the same period 87 children who had had diphtheria were selected for reference to the Rheumatism Clinic, of whom 43 showed evidence

Year	1931	1932	1933	1934	1935	1936	1937	1938	1939
After scarlet fever	30(11)	19(10)	16(11)	15(9)	19(16)	15(8)	3(1)	10(3)	4(0)
After diphtheria	—	16(11)	13(10)	11(7)	3(1)	9(6)	9(3)	13(4)	13(1)
Total referred after scarlet fever	131 (69)								
Total referred after diphtheria	87 (43)								
Figures in brackets are the number found to have cardiac defects.									

Fig. 6. Walthamstow Rheumatism Clinic. 1931—1939. Cases of suspected rheumatism referred from infectious disease clinic.

of heart disease. The institution of a follow up of children after scarlet fever and diphtheria presented no administrative difficulty, and the results indicate that the work was of value in detecting early cases of cardiac mischief.

To summarise: Use should be made of the knowledge that there is often an interval of one to three weeks between pharyngitis and subsequent rheumatism, in order to establish a national system of follow up examination of children a month after the illness of a sore throat. A pilot enquiry into the value of such a system for children who have had scarlet fever and diphtheria had borne fruitful results.

The prevention of sore throats by means of sulphonamide in children who are known to be rheumatic has proved of practical value, and should be employed until an easier method of prevention is discovered.

The time interval of one to three weeks between pharyngitis and subsequent rheumatic fever would seem to offer the ideal opportunity for prevention. The value of salicylate in this period is worth further study.

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Abstract of the Communication

given by Dr. K. Tallerman, London.

Dr. Tallerman said that he wished to comment on the decreasing incidence of rheumatic disease in childhood, as noted at his Hospital. Although he had been quite unaware of what the previous speaker, Dr. Sheldon, had intended to say prior to his paper,

he wished from his own experience to corroborate what had been said regarding the fall in the number of rheumatic cases.

As long ago as 1930 J. A. Glover had referred to acute rheumatism as an obsolescent disease. From the drop in numbers of rheumatic cases occurring in the armed forces, the fall reported in the incidence among London Elementary School Children, the drop in admissions to London County Council hospitals for rheumatism, and in out-patient attendances at Supervisory Centres, and from a similar trend at various centres, such as, the Bristol Cardio-Rheumatic Clinic, the Hospital for Sick Children, Great Ormond Street, London, at Glasgow and elsewhere, such as view as that expressed by Glover seemed to have much force.

Dr. Tallerman said that he was much struck by the infrequency with which he now encountered cases of this disease, as compared with the days when he was a student and a junior resident, and even a few years before the war.

He gave figures and showed charts based on the number of admissions of children under 14 years of age to The London Hospital, London, and of children attending the Children's Department of this hospital during the years 1937 to 39 and 1945 to 47, which showed that the percentage of rheumatic cases to total admissions or out-patient attendances had fallen by half in the latter, as compared with the former period. Out of a total of 1431 admissions from 1st June, 1937, to 31st May, 1939, there were 129 cases of rheumatic disease (acute and sub-acute rheumatism, established rheumatic carditis, and chorea); from 1st June, 1945, to 31st May, 1947, out of 743 admissions there were only 40.

For out-patients in the same periods the figures were respectively 2 836 new attendances and 66 total rheumatic cases (1937 to 39) and 1886 new attendances and 14 rheumatic cases (1945 to 1947).

Incidentally the *total* admissions and out-patient attendances had decreased very considerably since September 1939, as seen from the above figures for total admissions and out-patient attendances. This is due to factors connected with the War, such as devastation of large housing areas. Actually the school population in the area mainly served by The London Hospital had fallen by

32 399 in July 1946, as compared with July 1939, which represents almost exactly a 50 per cent drop in the school population.

Dr. Tallerman was not prepared to offer any definite explanation of the fall in incidence of rheumatic disease, which, however, he considered a matter of much interest, and one that called for further observation and study.

La enfermedad reumatica en la Republica Argentina.

Por los Dres. Prof. **José María Macera** y **Alberto P. Ruchelli**,
Buenos Aires.

En la encuesta sobre la enfermedad reumática del niño en América, publicado por el Departamento de Salud del Instituto Internacional Americano de Protección a la Infancia, se establece en forma subsinta los resultados obtenidos en nuestro país.

Habiéndonos ocupado en forma particular sobre el tema desde el año 1932, pudimos acopiar una vasta información en lo que respecta a la frecuencia en la Ciudad de Buenos Aires, de la enfermedad reumática en la infancia y sus secuelas cardíacas, efectuando estudios clínicos y estadísticos sobre morbilidad y mortalidad infantil producida por esta enfermedad.

Por el trabajo titulado «Mortalidad infantil por cardiopatías reumáticas» (José María Macera y Guido Costa Bertani), se demostró que en el año 1934, habían fallecido en el país 920 niños en la edad comprendida entre 1 y 15 años, por afecciones cardíacas reumáticas, superando en ese año a la mortalidad por difteria, que fué de 762 casos y ocupando el primer rango entre las enfermedades causantes de mortalidad.

El porcentaje de morbilidad infantil por cardiopatías reumáticas en nuestro medio hospitalario, fué puesto de manifiesto en el trabajo que presentamos a la Sociedad Argentina de Pediatría, titulado: «Concurrencia de niños reumáticos con y sin cardiopatía a los hospitales de la Capital Federal en el año 1938». Este trabajo reveló que sobre 1 100 niños reumáticos atendidos en solo 16 hospitales del Municipio, 649 eran portadores de francas

cardiopatías reumáticas, y que sobre el total de niños hospitalizados en el Hospital de Niños, de la Capital Federal por afecciones generales, el 10.71 % correspondían a niños reumáticos, y el 7.33 % a cardiopatías reumáticas.

En el Hospital de Clínicas, en el Instituto de Clínica Pediátrica de nuestra Escuela de Medicina, el 3.31 % de los niños concurrentes a los Consultorios Externos eran reumáticos.

Hemos establecido el índice de cardiopatías en el Medio Escolar de la Capital Federal, por un estudio que fué realizado con el mayor rigorismo científico, examinando a 10 000 escolares; se utilizaron los métodos y gráficos mas modernos, que tanta precisión han dado a las investigaciones diagnósticas sobre las alteraciones del corazón. Esta investigación reveló la existencia de 240 niños con cardiopatías, de las cuales correspondió el 2.01 % á cardiopatías adquiridas y el 0.39 % a las congénitas.

Un hecho de alta significación social, que surge de nuestro estudio, es el que el 0.64 % de la población infantil del país acusó una carditis reumática primitiva, es decir: se trataba de niños portadores de evidentes cardiopatías, pero con la particularidad de que nunca acusaron manifestaciones articulares; niños que eran y serán considerados como sanos, mientras no sean sometidos a un buen exámen cardiológico, o mientras no aparezcan en ellos manifestaciones articulares ó de insuficiencia cardíaca que la denuncien. Este tipo de cardiopatía fué un hallazgo ocasional en nuestra investigación, que motivó sorpresas de parte de los respectivos padres al enterarse de estos hechos; de ahí el alto significado médico-social que nosotros asignamos a este tipo de cardiopatías primitivas, ya que hasta el presente, de acuerdo a la bibliografía consultada se puntualiza su existencia, pero nó su frecuencia.

Nuestra investigación revela que su frecuencia es de 26.66 % sobre el total de las 240 cardiopatías encontradas entre los 10 000 niños examinados, es decir, mas de la cuarta parte de ellas, y que corresponde al 0.64 % de la población infantil del país.

Del mismo modo se han encontrado 82 casos de cardiopatías en potencia, que corresponde a un 34.16 % sobre las 240 cardiopatías estudiadas, ó sea un 0.82 % sobre el total de los niños ex-

aminados. En la conclusión número 19 de nuestro trabajo dejamos constancia del alcance que nosotros otorgamos a este tipo de cardiopatía, y en el capítulo VIII, de nuestro libro «Las Cardiopatías en Nuestro Medio Escolar», exponemos en forma amplia el concepto actual de las cardiopatías basado en la evolución de varios años de observación de las mismas y nuestras ideas al respecto.

Otro hecho muy significativo obtenido de nuestra investigación, es el que todo niño portador de un soplo accidental, con ó sin antecedentes reumáticos debe ser sometido al estudio radiográfico y electrocardiográfico, para determinar si corresponde ó nó clasificarlo como una cardiopatía en potencia.

Hemos encontrado en un total de 70 niños portadores de soplos accidentales en los cuales se efectuó el estudio electrocardiográfico, en 11 de éstos (es decir en el 15.70 %) existían trastornos electrocardiográficos importantes) y en 10 (el 14.28 %) trastornos electrocardiográficos ligeros, acusando el 16 % de ellos antecedentes de reumatismo.

Por el estudio deductivo al generalizar el porcentaje del 2.40 % de cardiopatías al resto de la población infantil del país en edad escolar, se establece que: posiblemente existen 44 253 niños cardíacos en todo el territorio de la República, de los cuales 42 594 serían por cardiopatías orgánicas adquiridas y 1 659 por cardiopatías congénitas, correspondiendo a la Capital Federal 6 390 cardiopatías adquiridas, llegando a 8 532 si se incluyen las congénitas.

Se destaca un alto hecho de significación social y es que se calcula que solamente recibe asistencia médica hospitalaria en el Municipio de Buenos Aires el 9.36 % de los niños portadores de probables cardiopatías reumáticas. Por otra parte, nuestro trabajo plantea la sospecha de que existan en el país 78 735 niños portadores de soplos accidentales, de los cuales 12 361 se calculan que presentarían alteraciones electrocardiográficas de importancia, relacionando el 15.70 % a los 78 735 niños mencionados.

Por último establecemos que si se suman los 42 594 probables niños con cardiopatías orgánicas a los 12 361 probables niños con soplos accidentales, pero con importantes trastornos electro-

cardiográficos se llegaría a la cantidad de 54 955 niños con lesiones cardíacas en todo el país.

Enrique Beretervide en su Servicio del Hospital Alvarez, encuentra sobre 345 niños reumáticos, sobre un total de 4 994 niños internados durante 18 años, es decir el 6.8 %.

Alfredo Casaubón en la Sala III del Hospital de Niños, sobre un total de 2 906 niños internados, 297 eran reumáticos, es decir el 10 %.

La frecuencia se modifica con la edad, Arana y Kreutzer, a examinar 1 500 niños con afecciones cardíacas orgánicas encontraron reumatismo en el 60 %, anomalías congénitas en el 28 % y diversas otras causas en el 12 %; vale decir de cada 10 niños, 6 tenían enfermedad reumática, 3 anomalías congénitas y 1 una afección cardíaca de otra índole.

El Doctor Sloer encuentra en la Ciudad de Rosario de la Provincia de Santa Fé (Litoral Argentino), que las defunciones por enfermedades del corazón en niños de 5 a 14 años en relación al total de fallecidos, dá un promedio del 10.6 %, es decir, 134 niños fallecidos por enfermedad reumática y cardíaca sobre un total de 1 273 defunciones, correspondiendo a la difteria 72 casos, enfermedad del aparato respiratorio 142, tuberculosis pulmonar 124, aparato digestivo 63 y otras enfermedades en general 738.

En la Ciudad de Santa Fé, Capital de la Provincia del mismo nombre, se encontró por estudios realizados en escolares, una frecuencia del 10 % de niños con manifestaciones reumáticas.

En la Ciudad de Córdoba (Hospital de Niños de la Sociedad de Beneficencia) se encontró sobre un total de 8 747 niños internados en el transcurso de 11 años, 336 niños afectados de enfermedad reumática y corea, vale decir el 3.8 %.

Como dato ilustrativo transcribimos cifras estadísticas sobre frecuencia de cardiopatías en general en nuestro país, comparadas con cifras de mortalidad por otras afecciones.

Las estadísticas oficiales por mortalidad demuestran que las afecciones cardíacas son la causa principal de mortalidad. El promedio de defunciones en nuestro país es en la actualidad de:

161 223 personas por año, de las que;

26 068 son causadas por afecciones cardíacas,

Numero de niños con enfermedad reumatica atendidos por primera vez durante los años 1938, 1942 y 1945 en los diferentes hospitales de la ciudad de Buenos Aires.—

Hospitales	Año 1938	Año 1942	Año 1945
De Niños	476	369	341
Brovato	149	146	119
Casa de Expósitos	86	79	39
T. Alvarez	36	57	114
Famos Mejía	39	53	94
Clínicas	114	53	49
Bawson	13	24	68
Salaberry	71	22	86
Zubizarreta	25	17	8
T. Alvear	14	16	58
Durand	32	11	20
J. Penna	—	—	18
Velez Sarsfield	—	—	63
Piñero	18	—	16
C. Argerich	—	—	23
Fernández	11	—	46
Totales	1 110	847	1 152

Cuadro comparativo de niños con enfermedad reumatica atendidos por primera vez durante los años 1938, 1942 y 1945 en los diferentes hospitales de la ciudad de Buenos Aires.

Por grupos de edades y sexo.

Edad	Sexo						Total			Porcentajes		
	Varon			Mujer								
	(1)	(2)	(3)	1938	1942	1945	1938	1942	1945	1938	1942	1945
	1938	1942	1945									
1 a 3 años	17	15	13	11	16	6	28	31	19	2.5	3.6	1.6
4 a 6 años	81	74	80	71	60	73	152	134	153	13.5	15.8	13.2
7 a 9 años	147	133	171	162	99	154	339	232	325	30.5	27.3	28.2
10 a 12 años	213	151	231	222	164	224	435	315	455	38	36.9	39.4
13 a 15 años	84	71	102	72	64	98	156	135	200	14	15.8	17.3
Totales	672	444	597	538	403	555	1 110	847	1 152	—	—	—

24 909 por afecciones pulmonares, sin contar la tuberculosis,
17 531 por enfermedades del aparato gastrointestinal,
13 850 por tuberculosis,
10 813 por cáncer,
10 604 con enfermedades del sistema nervioso,
8 921 por enfermedades infecciosas, sin contar la tuberculosis
y el resto de:
49 987 por causas de otra índole.

Esto significa los siguientes porcentajes de la mortalidad:

16 % afecciones cardíacas,
15 % afecciones pulmonares (sin tuberculosis),
11 % gastrointestinales,
9 % tuberculosis,
7 % cáncer,
6 % sistema nervioso,
5 % infecciones (menos tuberculosis),
31 % otras enfermedades.

Estas son las únicas cifras obtenidas hasta el presente en nuestro país, en lo que respecta a la frecuencia de la enfermedad reumática en la infancia de acuerdo a la bibliografía a nuestro alcance.

Tenemos informaciones que en el resto del país, y en diferentes zonas especialmente en las frías como la patagónica y andina, existe la enfermedad reumática en la infancia, pero no hay hasta ahora cifras estadísticas sobre la frecuencia de las mismas.

De acuerdo a la resolución de la XII Conferencia Sanitaria de Caracas, se recomendó que la enfermedad reumática se la considere de declaración obligatoria, creemos que en el futuro se podrán obtener estadísticas mas precisas que permitan conocer el alcance de la morbilidad y mortalidad de esta enfermedad en la infancia, en cada zona del país y así tener mas seguridad sobre la real frecuencia de este mal entre nosotros.

Buenos Aires, Junio 30 de 1947.

Essential Notions on Tuberculo-Rheumatic Disease (T.R.D.).

By **Ksawery Lewkowicz**, Kraków (Cracow), Poland.

Contrary to the teaching of RANKE, who assumed that tuberculosis as a whole — i. e. the tuberculosis lasting mostly from infection during childhood till the development of phthisis in adult or old man — constitutes one single, continuous disease, we now positively know that this continuum does not exist at all.

The main process of the T. R. D. consists in a succession of t. r. (tuberculo-rheumatic) septicaemiae appearing at varying intervals. Each of them is a separate, acute cyclic disease, i. e. a disease which starts from the state of health and returns to it. This cyclic course is undoubtedly due to the more or less strong immunization acquired during the disease by the infected organism. We are entitled, I think, to generalize this notion and to affirm that it is only in this way that antituberculous immunity can be gained. Parallely to the immunization a sensitization of the tissues to the tuberculoproteins arises and, as in consequence of the immunization the bacilli undergo a bacteriolysis and so their endotoxins are set free, these substances, acting on hypersensitive tissues, elicit strong, so called hyperergic reactions, which lead to the production of non-caseating inflammatory, or otherwise expressed, of rheumatic changes.

The initial t. r. septicaemia appears after the clinically symptomless incubation period of 3—7 weeks. It mostly presents itself, as it has long been known, as simple, often quite mild and short «initial tuberculous fever»; but sometimes it manifests itself in exanthematous form as initial erythema nodosum. The septicaemiae which appear later, after the initial fever having been passed through, ought to be designated as postinitial. The discrimination between the initial and postinitial t. r. septicaemiae is of actual importance. Indeed, the initial septicaemiae generally lead to a very strong immunization, probably never attained in this degree by the postinitial ones. This we must conclude firstly from its influence on the primary complex, which is speedily stopped in its growth, and afterwards solidly encysted, calcified or

even ossified; secondly from what we see in the initial erythema nodosum changes. Indeed we find there the incitants, mostly in more or less damaged coccoid forms, exclusively within the uni- or plurinuclear histiocytes, which seems to indicate that they are thus prevented from infecting other cellular elements. This preservation depends on the virginally intact state of the reticulo-endothelial (histiocytar) system and seems not to exist in this degree in postinitial septicaemiae, this system having been more or less damaged and exhausted through the foregoing septicaemiae. So the postinitial septicaemiae very often lead to the rheumatic involvement of various organs.

These septicaemiae may repeat themselves, sometimes even throughout the whole life of the patient, as recidives of erythema nodosum. The interval between two recidives may amount even to 20 or 40 years, but sometimes it is, on the contrary, as short as only two months. In the latter case we are compelled to admit that the formerly existing immunity must have very quickly diminished almost to zero, i. e. almost to the virginal normergy. In my opinion, we are entitled to generalize this notion and to state that antituberculous immunity is always very unstable.

The postinitial erythema nodosum is in about 40 % of cases combined with rheumatic involvement of joints or muscles. But we may also regard these cases as acute rheumatism with added erythema. Now, in the same conditions pure acute rheumatism also may evidently appear, forming a sort of erythema nodosum case, exhibiting rheumatic symptoms, but no exanthema. Its pathogenesis thus becomes plain. Moreover, our clinical investigations (chiefly X-rays and tuberculin tests) in about 50 cases of rheumatic children aged from 2 to 14, showed that it appears exclusively in children, who some months or even years ago — sometimes repeatedly — passed through any t. r. process.

Thus all true rheumatism proves tuberculous rheumatism, or, if we prefer the designation, Poncetian rheumatism.

In rheumatic changes the rheumatococcoid, i. e. a granular biologic variety of the tubercle bacillus can always be found as incitant. It appears in particularly copious quantities in peracute,

rapidly fatal cases. It is acidfast and thus colourable by the Ziehl-Neelsen method, but the decoloration should be cautious (not too strong).

Some New Notions on the Old »Classic« Tuberculosis.

By **Ksawery Lewkowicz**, Kraków (Cracow), Poland.

If — during the t. r. (tuberculo-rheumatic) septicaemiae — the elaborated immunity is quite insufficient, ordinary tuberculous changes (e. g. miliary tuberculosis, caries of the bones, arthroace, pulmonary phthisis) arise.

The source, from which the tuberculous septicaemic infections generally start, consists in any caseous changes, in the first place in those of the primary complex. Indeed, the antituberculous immunity, being cellular or tissular and not humoral, cannot extend on the necrosed areas. So the bacilli find in tuberculous cheese — which must be regarded as an infected foreign body, lying within the organism, but not appertaining to it — a safe shelter, where they can maintain their vitality and virulence for years together. This presence of the bacilliphorous caseous changes constitutes an important distinctive character of tuberculosis, as compared with other infectious diseases. It creates namely the conditions, through which tuberculosis as a whole is brought about, sometimes even in a forme, which may make the impression of continuous disease.

The disease ends then as tertiary, mostly pulmonary tuberculosis. In the course of the latter process erythema nodosum may sometimes appear, especially after the artificial pneumothorax having been established and thus a good encystation of the caseous changes obtained. This must be regarded as a proof, that the immunization which generally accompanies tertiary tuberculosis may sometimes decrease almost to virginal normergy. Indeed, only in that condition is a sufficiently copious multiplication of the incitants possible and consequently the formation of the gross lesions of erythema. But evidently the septicaemiae which repeatedly start from tertiary changes are mostly non-exanthematous, they

may be also quite mild and of short duration; they are then easily overlooked. Nevertheless, the immunity, demonstrable in tertiary period, is undoubtedly elaborated in their course. It constitutes by no means stable condition.

So called Catarrhal Jaundice is a Rheumatic Disease, as well as the Allegedly Epidemic Jaundice.

By **Ksawery Lewkowicz**, Kraków (Cracow), Poland.

There exist no clinical differences between the catarrhal and the epidemic jaundice. They both constitute one single disease, the etiology of which is still quite unclear. There may be, however, adduced some number of analogies between jaundice and rheumatism, indicating the close kinship of the two conditions.

1) Both are infectious diseases — this appears particularly obvious in their acute, pyrexial forms —, but they are not directly contagious; nevertheless they sometimes form little pseudo-epidemics.

2) They do not happen in the first year of life and are seen only very rarely in the second (see point 7).

3) The incitant of either was hitherto known and by some authors a specific virus was as such suspected.

4) Some authors (LÖWENSTEIN, REITTER, BERGER) obtained in high percentage of cases cultures of tubercle bacilli from the blood of rheumatic patients and similar bacteriologic results were repeatedly obtained by BEYER, RINNE and HAUSBRANDT in a case of jaundice, in which the underlying hepatitis passed into liver atrophy with subsequent cirrhosis.

5) A quite analogous case was examined post mortem by myself histologically. Rheumatococccoid infection of the liver was demonstrated. Similarly it was always found post mortem in my cases of typical rheumatic processes.

6) Heart lesions are very frequent in both diseases and are particularly easily demonstrable by electrocardiographic, but often also by radiographic examination.

7) In systematic investigations previous tuberculous infection was demonstrated through the results of tuberculin tests and of radiologic examinations of the lungs and their hila in all our 30 cases of jaundice and similarly in all our 50 cases of articular and cardiac rheumatism. It had generally preceded the rheumatic or hepatic manifestations for months or years together and the tuberculous changes appeared — when these manifestations arose — mostly quite radiologically inactive and containing calcifications, but sometimes also partly active. Clinically the patients were mostly regarded as having quite recovered from their tuberculous affections.

There is evidently a condition of mutual exclusion one another between rheumatism and tuberculosis. Tuberculous changes will prevail, if the antituberculous immunity is insufficient. Is it on the contrary sufficiently high, but not full, the tuberculous processes will be stopped in their evolution and rheumatic will arise.

In babies there are generally unfavourable conditions to obtain a sufficiently high immunization and, moreover, the time, necessary for the inactivation of their tuberculous changes, is wanting. They therefore do not fall ill either with rheumatism or with jaundice (see point 2).

Section 7—Endocrinology in Childhood.

A propos d'un cas de virilisme surrénal avec tumeur de la corticale surrénale et diabète insipide chez une fillette de 28 mois.

Par S. Bartsocas.

Directeur de la section infantile de l'hôpital «Evangelismos» d'Athènes.

Dans l'érudite et complète étude des M. M. Golstein AL, Seymour F. et autres, qui a été publiée dans le No 5 de Nov. 1946, in the American Journal of Diseases of Children, qu'il me soit permis d'ajouter un cas de plus de *Virilisme surrénal avec tumeur de la corticale surrénale et diabète insipide chez une fillette de 28 mois.*

Ce cas, qui est le seul qui ait été étudié en Grèce se présente comme suit:

Il s'agit d'une enfant de 28 mois nommée Marie Zach. Parents et un frère en bonne santé. Aucune tare héréditaire et notamment pas de tuberculose, d'alcoolisme ou de syphilis. Nourrie au sein normalement jusqu'au 6^{me} mois; poussée dentaire, premiers pas et premiers mots dans les délais normaux. S'est bien portée jusqu'à l'âge de 20 mois. A cet âge là, l'enfant a présenté une augmentation accélérée du poids du corps avec dépôt de graisse en particulier au visage, au thorax, au niveau de l'abdomen et des seins sans que cet état se soit précédé d'une autre affection ou de troubles apparents. Elle pèse déjà 14 kgr 300 au lieu de 12 000 gr et mesure 0 m 75 au lieu de 0 m 80 que l'on considère généralement comme étant des mesures normales. Les membres inférieurs sont de longueur légèrement diminuée. Périmètre de la tête à 0.47, et du thorax à 0 m 55. Les seins (1^{ère} photo) sont développés comme s'il s'agissait d'une fillette de 8 à 10 ans; on y note en outre une légère proéminence des mamelons. En ce qui concerne les organes génitaux externes, on a l'impression qu'il s'agit d'une vulve d'une fillette de 13 à 15 ans. De nombreux poils existent déjà sur le mont de Venus. Les grandes et petites lèvres développées comme chez une enfant de 15 ans. Le clitoris est hypertrophique et a une longueur de 1 cm. et davantage. L'hymen de forme arrondie se dessine normalement. L'examen des organes génitaux internes au toucher rectal bimanuel ne montre rien de particulier.



Fig. 1.

La jeune enfant a présenté une menstruation unique et de la durée d'une seule journée. Elle présente également des poils au niveau de la lèvre supérieure, au thorax, aux cuisses et aux mollets (photos 2 & 3).

Les sourcils sont denses. Les cheveux sont secs et clairsemés par suite d'une chute. Le cou est court. La peau est sèche. Les muscles bien développés. La force musculaire augmentée. La voix grave. Son développement intellectuel est celui d'un enfant plus âgé. Sa dentition est régulière. En ce qui concerne le caractère de la jeune enfant on note qu'elle est actuellement tranquille, obstinée et irascible tandis qu'elle était auparavant vive et toujours en mouvement. Quant aux systèmes respiratoire et nerveux il n'y a rien de bien spécial à signaler.

La palpation de l'abdomen dont le périmètre est de 65 cm donne l'impression de l'existence d'une tumeur dans la région hypochondriaque gauche.

La pression artérielle est de 18 max. 11 min. Dès le 24^{me} mois, la

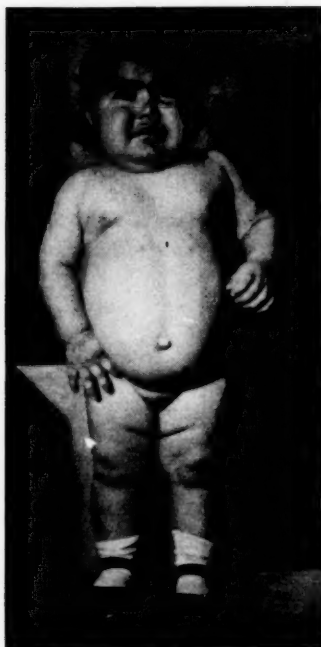


Fig. 2.

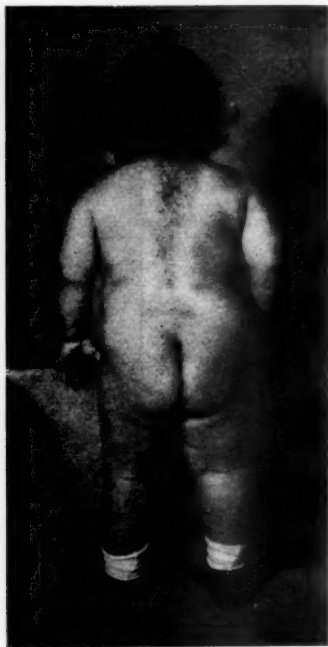


Fig. 3.

jeune enfant a présenté une polyurie sans présence de sucre avec polydipsie. La quantité d'urines émises dans les 24 heures est d'environ 4 000 grs, dont le poids spécifique est de 1 005. Il s'agit donc d'un diabète insipide. Il est compréhensible qu'à cause de la grande quantité d'urine émise, l'enfant boive de l'eau en abondance, possédée, qu'elle est par une soif insupportable. A l'examen des urines, nous n'avons pas trouvé d'autres éléments pathologiques sauf la diminution du poids spécifique susmentionné. La réaction de Wassermann dans le sang a été négative. La réaction à la tuberculine selon von Pirquet, négative également. Les radiographies des diverses régions du squelette présentent une ostéogénèse plus avancée que la normale. Le crâne est régulier. La selle turcique ne présente rien d'intéressant.

Rien en ce qui concerne l'examen des yeux. Le taux de sucre dans le sang est de 0.91 %, le calcium selon Vaard de 9.8 mil. %, phosphates à 0.003 %. Globules rouges 3 500 000, hémoglobine 65, avec index 0.92.

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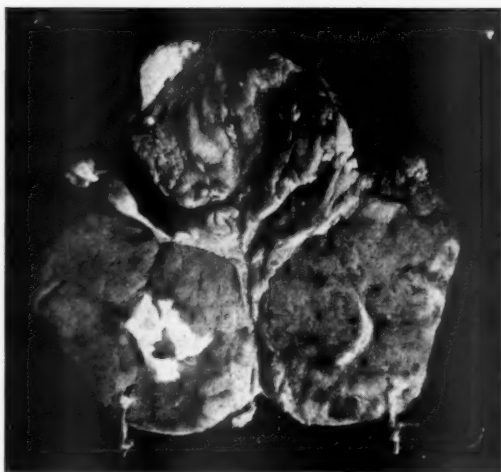


Fig. 4.

Leucocytes 7.800, repartis comme suit: 3 % d'éosinophiles, 1 % noyau en bâtonnets, 64 % noyau polymorphe et 32 % lymphocytes; temps de saignement 2', temps de coagulation 7'.

Le métabolisme basal a été trouvé légèrement augmenté.

Etant connu que ce syndrome est dû à une tumeur de la surrénale et que son excision amène dans bien de cas une diminution de l'ensemble des symptômes, nous avons adressé la jeune enfant pour opération d'excision de la tumeur de la surrénale gauche. A cette opération, il a été découvert une tumeur de la grosseur d'une orange siégeant au niveau de la surrénale gauche.

L'examen histologique de la tumeur faite par Monsieur le Professeur Katsaras est le suivant:

La tumeur surrénalienne envoyée est de la grosseur d'une orange de dimensions moyennes. Sa forme a été triangulaire. Son poids a été de 195 gr. La surface de la tumeur est abondamment lobée, avec de nombreux lobules hémisphériques de la grosseur d'un noyau de cerise jusqu'à celle d'une noisette. A la coupe, la consistance de la tumeur est molle, uniformément myéloïde, de couleur brun-cendré.

Par cet examen microscopique, il a été démontré que le néoplasme se compose de cellules de grandeur moyenne, de forme

cuboïde, polygonale ou ronde suivant leur disposition réciproque.

Le noyau est rond avec un réseau de chromatine dense et un nucléole. Le protoplasme est de couleur claire. Les cellules néoplastiques sont disposées en travées entre lesquelles on note la présence d'un réseau serré de capillaires sanguins.

En général, le néoplasme montre les caractères d'une glande endocrine et présente généralement l'image caractéristique de la corticale surrénale. Les cellules néoplastiques sont homogènes. On ne remarque pas de mouvements nucléaires. Il s'agit d'un adénome de la substance corticale de la surrénale.

Seize heures après l'opération la petite est décédée et malheureusement il n'a pas été possible de procéder à l'autopsie.

En ce qui concerne le diabète insipide il est possible qu'il soit dû à des troubles de la neuro-hypophyse ou du Diencéphale ou qu'il soit idiopathique, comme il n'est pas exclu qu'il ait une certaine relation avec le syndrome actuel.

En résumé: Nous avons cru utile de communiquer ce cas, d'une part parce que ces cas, surtout à un âge si jeune, sont rares, et d'autre part à cause de la confirmation du diagnostic par la découverte de la tumeur surrénalienne et de ses rapports avec un diabète insipide. Résumant ce que nous avons décrit ci-dessus nous notons ce qui suit: Sur une jeune enfant de 28 mois se portant bien jusqu'à l'âge de 20 mois s'est développé une adiposité, hirsutisme du type masculin, un grand clitoris avec apparition des autres caractères génitaux et augmentation de la tension artérielle. A l'opération, il a été excisé au niveau de la surrénale gauche une tumeur dont l'examen histologique a révélé la présence d'un adénome de la corticale de la glande surrénale. Ces trouvailles anatomo-histologiques confirment pleinement le diagnostic de virilisme surrénalien et il se confirme une fois de plus que ce syndrome est dû à une tumeur de la surrénale. Ce syndrome a coexisté avec un diabète insipide.

Late Complications of Juvenile Diabetes.

By **A. L. Chute**, M. A., M. D., Ph. D.

From the Wards and Laboratories, Hospital for Sick Children, and the Department of Paediatrics, University of Toronto, under the direction of Alan Brown, M. D., F. R. C. P. (Lond.).

Introduction.

1946 marked the 25th anniversary of the discovery of insulin. It seemed appropriate therefore to review the records of the Juvenile Diabetics who had passed through the clinic of the Hospital for Sick Children in Toronto. It is chiefly with this survey that the present paper deals.

The study was limited to those cases who contracted the disease during the period 1922—1932. Thus all surviving cases have had their disease for at least 15 years. In presenting these figures it should be borne in mind that the data represents the results obtained during the early insulin period when many of the problems of insulin dosage, acidosis and dehydration were not clearly appreciated, and when chemotherapy was not available for the control of infection. Furthermore, all these patients have graduated from the care of the Hospital some years ago as our age limit is 14 years. Unfortunately, not a few have failed to avail themselves of proper supervision at adult clinics or from their personal physicians.

Incidence.

One hundred and twenty-three cases of diabetes were seen in the Hospital in the first decade following the discovery of insulin. The first slide (Table 1) indicates the present status of these patients.

TABLE 1.

		Total	%
<i>Living</i> —	1. Examined	27	
	2. Replied to questionnaire	20	47
	3. Indirect evidence of survival	5	5
		52	42
<i>Dead</i> —	1. Died in H. S. C. ¹	26	
	2. Died elsewhere	32	58
<i>Not traced</i> —	13	13
		123	10

¹ Hospital for Sick Children.

Treatment and Control.

The average daily dose of insulin for the 47 living diabetics is 48 units. The lowest dose is 20 units and the highest 120 units daily.

14	individuals	take	only	Toronto	(regular)	insulin
9	»	»	»	Protamine	Zinc	insulin
24	»	»	»	both in varying proportions		

Only 5 of these patients still weigh their diets, a few measure the diet, the majority merely judge it by appearance and avoid excess starches, sweets and pastries. Half of them still test their urine at more or less regular intervals; half do so only when ill. Half of them see their physician regularly; the remainder have not seen their physician for from 2 to 15 years, and then only for severe illness.

Mortality.

Table 1 indicated the total mortality as 47 %. Table 2 (Slide 2) indicates the causes of death according to the length of survival after the development of diabetes. Coma heads the list by a large margin in all groups and accounts for 37 of the 58 deaths, or 64 %. Nephritis was the chief cause of death in 3, and a contributory cause of death in a further 3 cases. Degenerative myocarditis was the chief cause in one and the contributory cause in 2 deaths. Pulmonary and other infections account for many cases but all of these succumbed before the days of chemo-therapy. One can not refrain from paying tribute to the brave soul who concealed his disease, entered the army, and gave his life for freedom on the battlefields of France.

Slide III, taken from Dr. Joslin's records at the George F. Baker Clinic in Boston, illustrates the progressive decline in the incidence of deaths from coma since the discovery of insulin, but also indicates the rising incidence of deaths from degenerative lesions due to arteriosclerosis, such as nephritis and myocarditis.

Late Complications in Juvenile Diabetes.

The complications seen in the 27 cases who submitted themselves for examination are set out in Tables 3 and 4. Table 3

TABLE 2. Causes of Death in Relation to Duration of Diabetes.

Causes	Under 15 years		15—20 years		Over 20 years		Total	
	Chief	Sec- ond- ary	Chief	Sec- ond- ary	Chief	Sec- ond- ary	Chief	Sec- ond- ary
Coma	32		3		2		37	
Acute Pancreatitis ..	1						1	
Insulin Reaction ..	2						2	
Nephritis	3	2				1	3	3
Myocarditis				1	1	1	1	2
Pneumonia	1	6		1			1	7
Influenza	1	4					1	4
Bronchiectasis		1						1
Pulmonary								
Tuberculosis		2						2
Septicaemia	2						2	
Carbuncle			1				1	
Cellulitis		1						1
Measles		1						1
Pertussis		1						1
Intestinal								
Intoxication		1				1		2
Accidental	1				1		2	
Killed in Action ..					1		1	
Unknown	4		2				6	
Total	47		6		5		58	

shows the incidence and nature of the complications in those who have had diabetes 15 to 20 years. Table 4 shows the same findings for those who have survived 20 or more years since its onset.

TABLE 3. Juveniles Surviving 15 years. But less than 20 years.

Complications in 14 of 23 living cases.

	9 males	5 females	Total	%
Eyes Retinal Haemorrhage	2	1	3	21
Retinal Exudate	3		3	21
Lens Opacity		2	2	14
Hypertension	1		1	7
Albuminuria	1	2	3	21
Arteriosclerosis (X-ray legs)	1	1	2	14
Neurol (absent knee or ankle Reflexes)	2	1	3	21
No demonstrable Disease	5	2	7	50

TABLE 4. Juveniles Surviving 20 years of Diabetes.

64 cases of Diabetes were admitted to H.S.C. from 1922 to 1926 inclusive.
29 of these cases survived for 20 years or more 45%.
24 are still alive.

Complications in 13 of the 24 living cases.

	7 males	6 females	Total	%
Eyes Retinal Haemorrhage	4	1	5	38
Retinal Exudate	4	1	5	38
Lens Opacity	3	1	4	31
Heart Enlargement	2		2	15
Hypertension ¹⁶⁰ / ₁₀₀	3	1	4	31
Albuminuria	4	1	5	38
Arteriosclerosis	2	2	4	31
Bronchiectasis		1	1	8
Epilepsy		2	2	15
Absent Reflexes (Knees or Ankles)	3	3	6	46
No Demonstratable Disease	1	1	2	15

The high incidence of vascular disease as evidenced in retinal changes, hypertension, albuminuria and arteriosclerosis of the peripheral vessels is in agreement with the findings of previous reports by various writers. That the incidence increases with the duration of the disease is clearly shown by the two tables. These findings are the more striking when one remembers that the oldest in this series was only 40 years of age and the youngest 22 years of age. The average was 29 years.

The following slides illustrate a few of the lesions which were present.

The first slide shows cardiac enlargement in a young farmer 24 years of age who had had diabetes for 20 years. This boy had been on virtually a free diet for 15 years. His blood pressure was 170/120. His urine boiled solid with albumin. He had lens opacities and marked retinal changes. The next slide illustrates the marked arterio-sclerosis of his legs. The dorsalis pedis pulsation was absent in both feet.

The following x-ray is that of a 31 year old girl who had had diabetes for 20 years. She too had maintained indifferent control of her diabetes. This patient also had marked albuminuria and suffered from pernicious anaemia and bronchiectasis.

The next two slides illustrate some of the ocular changes. The first demonstrates the appearance of a typical diabetic cataract. No cases were seen in our series which showed these findings. The opacities seen were of the senile variety.

The next slides illustrate some of the types of haemorrhage seen in diabetic retinitis. Unfortunately, the commonest, which is the small deep punctate haemorrhage in the retina, is not represented here. The subhyaloid haemorrhages may clear spontaneously or they may rupture into the vitreous. This leads to fibroblastic proliferation and organization, causing the condition called retinitis proliferans.

Besides the physical handicaps, one was impressed with the psychological problems presented by a fair percentage of this group. However, time does not permit for elaboration here.

Discussion.

Following the introduction of insulin and the gradual realization that adequate caloric intakes could be safely maintained by its use in children, hope spread that a complete answer had been found to this previously fatal disease. However, with the prolongation of the diabetic life, other baffling complications have arisen. Thus White (2 a) reports that in 249 juveniles who survived 20 years, »the significant and disturbing complications were arteriosclerosis, retinitis and nephritis». Arteriosclerosis was present in 70 %, retinal haemorrhage in 65 %, retinal exudate in 50 %, hypertension in 40 %, albuminuria in 35 %, and retinitis proliferans in 8 % of those examined.

Rosenbusch (4) emphasizes nephropathies, tuberculosis, polyneuritis, eye complications, and retardation of growth in a series of 88 cases he studied.

The present series reveals essentially the same picture. The problem which naturally arises therefore is whether insulin is the complete answer or whether there are other as yet undiscovered causes responsible for the appearance of these vascular complications. There are those who support the theory that strict physiological control together with emphasis on certain aspects of diet will prevent the appearance of these conditions (3) (6). As

yet no group with 15 years or more survival under such ideal conditions has been reported. Indeed the pendulum has swung to the other extreme and some clinics advocate free diets with sufficient insulin to prevent ketosis and symptoms without any attempt to keep the blood sugar within normal limits.

If these complications are due to the effects of inadequately controlled carbohydrate metabolism, then much more strenuous efforts should be made to protect these unfortunate individuals from becoming incapacitated and cut off in the prime of life. If they are caused by other factors such as an error in fat metabolism or deficiency of sex hormones, or the production of a specific toxin, then meticulous regard to the blood sugar levels may be only an unnecessary and extremely onerous burden.

An answer to this problem is urgently required but until conclusive evidence is forthcoming it would appear to be the part of wisdom to maintain the blood sugar as close to normal limits as is reasonably possible.

To facilitate this and to ensure continuity of care for juvenile diabetics after graduation from the paediatric age group, some organization, preferably the Department of Health, should assume the responsibility of keeping in contact with these persons and provide if necessary for their supervision and treatment. A diabetic service similar to the tuberculosis service offered by many States could do a great deal to prevent unnecessary illness such as coma and infections, and might through constant supervision prevent or delay the appearance of the vascular complications.

Summary.

1. A review of 123 juvenile cases developing diabetes prior to 1932 is presented. Fifty-two are living, 58 are dead, and 13 have not been traced.

2. Twenty-nine cases survived for 20 years; 24 of these are still living. These show marked evidence of degenerative lesions, arteriosclerosis, albuminuria and retinitis. These findings are present in the 15-year group to a lesser degree.

3. The problem of control and prevention of these complications is discussed.

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Le syndrome pseudo-basedowien de la puberté.

Par Robert Clement, Paris.

A la puberté on observe un syndrome que, malgré quelques signes communs, il ne faut pas confondre avec la maladie de Graves-Basedow ou l'adénome toxique, car il en diffère par de nombreux points.

A côté des formes frustes de la maladie de Basedow, des «basedowoides de Stern», des manifestations parabasedowiennes et du «syndrome sympathique basedowiforme», des syndromes d'hyperthyroïdie frustes, il faut faire une place à part au syndrome pseudo-basedowien de la puberté en raison de l'âge d'apparition, du complexe endocrinien au milieu duquel il se manifeste, du métabolisme de base diminué ou normal, du pronostic et de la thérapeutique qu'il comporte.

Ces faits sont connus des pédiatres car ils ne sont que l'exagération d'un état physiologique. Cependant les observations publiées sont rares et un peu différentes¹, il s'agit d'enfants beaucoup plus jeunes. Cas de Jean Hutinel, L. Lebée et R. Testard (1927) de tachycardie chez un enfant de 10 ans, avec métabolisme normal; de R. Marquézy et Mlle Jammet (1931), de «goitre et exophtalmie chez un enfant de 4 ans, avec métabolisme normal»; de Mouri-quand, L. Weil et Mme Enselme (1933), de «goitre avec exophtalmie sans modification du métabolisme basal chez une fillette de

¹ Nous nous excusons du peu de références anglo-américaines, mais celles-ci nous ont manqué depuis 6 ans.

9 ans». H. Janet donne une courte description du syndrome sous le nom de «goitre simple de l'adolescence» dans le *Traité de Médecine des Enfants* (1934); Azerad y consacre quelques lignes dans les «goitres de l'enfance» (*Encyclopédie médico-chirurgicale*, 1936). Mais il y a intérêt à attirer l'attention sur ce syndrome, qui fait croire parfois à une hyperthyroïdie et provoque des erreurs de traitement. Son étude est susceptible d'apporter des éclaircissements sur d'intéressants problèmes pathogéniques encore en discussion et sur le rôle des diverses hormones et du système sympathique dans le développement du goitre, de l'exophtalmie, de la tachycardie, des acrocyanoses et des troubles psychiques.

Sa fréquence s'oppose à la rareté de la maladie de Basedow à cet âge: nous avons pu en observer une trentaine de cas en 9 ans¹ contre 2 hyperthyroïdies et 3 goitres chroniques simples ou héréditaires.

Il s'agit presque toujours de jeunes filles (29 F. et 2 G.), entre douze et quinze ans, en pleine évolution de puberté. La plupart viennent de subir une poussée de croissance staturale et ont une taille au-dessus de la normale (80 p. 100). L'hyperthyroïdie staturale parfois notable (jusqu'à 22 centimètres au-dessus de la moyenne), porte surtout sur les membres, ce qui leur donne souvent un aspect élancé. Le poids est variable (dix-neuf fois au-dessus, dix fois audessous des moyennes de Nobécourt. Le rapport Poids sur Taille est augmenté dans 59 p. 100 des cas. Les caractères sexuels secondaires sont déjà marqués, les seins bien formés, les poils pubiens et axillaires fournis. Dans un cas seulement, il y avait retard considérable de la pilosité axillaire chez une fille réglée régulièrement depuis deux ans. Les règles sont normales ou abondantes.

L'hypertrophie du corps thyroïde, toujours nette, n'est pas très volumineuse; en général totale, elle prédomine parfois d'un côté; sa consistance est élastique, homogène, non nodulaire; elle n'est pas pulsatile. Son installation, le plus souvent insidieuse, se fait parfois brusquement, à la suite d'une émotion dans les jours qui précèdent les règles. Dans un cas, la jeune fille nous a été

¹ On trouvera la plupart des observations dans la thèse de Paul Reynes (Paris 1939, n° 1311, J. Peyronnet et C°, édit.).

amenée pour des phénomènes d'oppression et de gêne respiratoire qui paraissent plus subjectifs que dûs à une compression de la trachée.

La tachycardie est à peu près constante, mais elle n'atteint pas des chiffres élevés (en moyenne 110—120 P.) et varie suivant les examens. Elle s'exagère avec l'effort et diminue très franchement par compression des globes oculaires. Il y a surtout instabilité du pouls et parfois éréthisme cardiaque.

Le tremblement, menu, demande à être recherché et manque dans la moitié des cas.

L'exophtalmie marquée est rare, nous ne l'avons notée que deux fois; elle ne s'accompagne pas de signes oculaires. Le plus souvent, l'exophtalmie est légère avec éclat et vivacité du regard.

Les troubles du caractère et de l'affectivité sont constants: instabilité, émotivité, inaptitude à fixer l'attention, anxiété, irritabilité. Dans quelques cas, ils prennent l'allure d'un véritable état psychique.

Les troubles vaso-moteurs à type d'acrocyanose et d'acroasphyxie font partie intégrante du syndrome et sont surtout marqués au niveau des genoux, de la face externe des jambes et des mains; ils n'atteignent que rarement la face.

Ce syndrome, qui pourrait en imposer pour une maladie de Basedow, en diffère par l'absence de signes de toxicité: pas d'amaigrissement, bien que quelquefois la courbe de poids soit stationnaire, pas de diarrhée et surtout le métabolisme basal, au lieu d'être augmenté, est abaissé ou normal.

L'abaissement du M. B. atteint fréquemment 30 p. 100. On pourrait se demander si ces résultats ne sont pas faussés par la taille ou le poids des sujets. Mais les résultats viennent de laboratoires différents et les corrections nécessaires ont été faites. Ces chiffres sont d'autant plus remarquables que le métabolisme basal est généralement augmenté à cet âge. D'après Dubois, Gottsche, Peting, Lax, le métabolisme serait augmenté de 25 p. 100 à la puberté. Mouriquand, J. Enselme et Mme Enselme, sur 50 enfants porteurs de goitre, dont 43 filles, ont trouvé le métabolisme normal dans 17 cas, augmenté dans 20 et diminué dans 13. Il revient progressivement à la normale en même temps que disparaissent la

	Age	Thyroïde	Pouls	Tremble- ment	Exophtalmie	Amalgisse- ment	Diarrhée
G., Heloise	13.5	+	84	+	0	0	0
G., Christiane	14.5	+	108	+	0	0	0
G., Lucienne	14.5	+	112	+	0	+	0
			110				
			98				
	15.5	-	88	0	0	0	0
K., Marie	12.5	+	118	0	0	0	0
R., Christiane	15	+	120	+	+	0	0
S., Jeanne	14	+	120	0	+	0	0
B., Carmen	13.5	+	96	+	0	0	0
	15	+	108	0	0	0	0
	16.5	-					
G., Renée	11	+	104	+	0	0	0
	11.5	+		+	0	0	0
E., Anne-Marie	14.5	+	84	0	0		
S., Simone	15	+	104	+	0	+	0
J., Suzanne	13	+	90	0	+		0
	15.5	+	80	0	+		0
M., Marie-L.	14.5	+	115	0	0	0	0
	16.5	+	84	0	0	0	0
F., Ginette	12	+	80	+	0	0	0
	12.5	+	72		0	0	0
S., Adriné	8	+	120		0	0	0
H., Janine	13	+		0	0	0	0
	18.5	-	80	0	0	0	0
L., Madeleine	14.5	+	104	0	0	0	0
A., Yvonne	14.5	+	120	+	0	0	0
C., Louise	14	+	104	+	0	0	0
S., Denise	15	+	100	+	0	0	0
B., Yvette	14.5	+	128	+	0	0	0
			92				
L., Ma	14.5	+	104	0	+	0	0
B., Suzanne	13	+	100	0	0	0	0
S., Pierrette	12	+	112	0	0	0	0
B., Andrée	14.5	-	100	0	+	0	0
S., Solange	8	+	128	0	0	0	0
	11	+	160	+	0	0	0
S., Lucienne	11.5	+	90	0	0	0	0
	14	+	96	0	0	0	0
C., Maud	16	+	110	0	+	+	0
M., Christiane	18.5	+	112	0	0	0	0
P., Guy	13	+	92	0	0	0	0
	13.5	+	124	0	0	0	0
	14	+	120	0	0	0	0
H., Claude	15	+	100	+	+	0	0

Tr. vaso- moteurs	Tr. pay- chiques	Régles	Mét-basal	Taille	Ecart	Poids	Ecart	Rapport P/T	Ecart
+	+	N	-24	161	+13	53.6	+ 5.1	332	+ 70
+	+	N	-25	154	+ 5.7	48	+ 5.7	318	+ 39
0	+	I	-29	156	+ 5	49.2	+ 6.9	315	+ 36
			-17	156		47.7			
			-18	156		50			
0	0	N	N	157	+ 5	52.8	+ 8.3		
+	0	N	-30	145	+ 8	42.7	+ 6.7	294	+ 48
+	+	I	-10	158	+ 6	51.2	+ 7.3	324	+ 38
	0	N	N	151		37	- 3.8	245	- 27
+	+	A	-18	148	+ 5	38	- 0.5	256	- 6
+	+	A	-24	149		39.6			
0	0	A	N	151	- 3	45.2			
+	+	0	-11	154	+21	43	+13.1	279	+ 59
+	+	0	- 6	155	+20	47.1			
+	+	N	-37	156	+ 6	49	+ 6.7	314	+ 35
+	+	N	-14	143	- 8	40	- 3.9	279	- 7
		N	-38	164	+22	50.1	+13	305	+ 52
		N							
+		A	-23	154	+ 3	52	+ 9.7	337	+ 58
		N		155		55.4			
+	+		-17	137	+ 1	26.5	- 7.5	197	- 46
			-19	138		26.7			
	+		N	127	+11	23.9	+ 3.5	188	+ 13
+	+	0	-17	164	+24	58.4	+21.4	356	+103
+	0	N	-17	179		64.8			
+	0	N	-11	153		43	+ 0.7	281	+ 2
0		N	N	157	+ 6	40.5	- 1.8	257	- 22
+	0	N	N	151	+ 1	39.5	- 1.3	261	- 11
0	+	N	-10	147	- 6	40	- 3.9	272	- 14
+	+	A	N	151		52.6	-10.3	348	+ 69
	0	N	-11						
0		N	-11	157	+ 6	48	+ 5.7	305	+ 26
0	+	I	-16	145	+ 3	32.8	- 4.2	226	- 27
+	+	0	-19	142	+ 4	33.4	- 0.6	235	+ 15
+	+	0	-20	150	- 1	32.2	-10.1	214	- 65
+	0	0	N	124	+ 8	24.7	+ 4.3	199	+ 24
+	+	0	- 8	151	+16	39.8	+ 9.9		
		0	N	147	+10	37.1	+ 4.9	232	+ 23
+	+	N	-22	160	+11	52.8	+12		
+	+	N	-27	169	+16	48	+ 2.6	284	- 12
	+	N		162	+ 7	51	+ 2	314	- 2
+	0		- 6	158	+16	46.9	+12.3	296	+ 58
+	+		-20	164	+20	49.8			
	0		-20	166	+20	50.2			
0	0	N	N	160	+ 3	40.5	- 4.9	254	- 31

plupart des symptômes. La tachycardie et les manifestations psychiques sont les dernières à s'effacer. L'évolution est spontanément favorable, en quelques mois, voire en quelques semaines.

Le goitre pseudo-basedowien de la puberté est aussi très différent des goitres endémiques. Il s'agit de jeunes filles minces, longues, ayant presque une taille au-dessus de la normale. Malgré l'abaissement du métabolisme basal, on ne peut parler chez elles d'hypothyroïdie en l'absence d'infiltration tégumentaire, de friabilité, de petits signes traduisant une insuffisance fonctionnelle de la thyroïde. Si ces enfants ont fréquemment de la difficulté à fixer leur attention, ils ont en général une grande vivacité intellectuelle, motrice et de caractère. La cholestérolémie et la lipidémie sont normales ou basses.

Le syndrome s'atténue et disparaît dès que les modifications physiques et physiologiques de la puberté ont achevé leur cycle et que le système neuro-endocrinien a trouvé son nouvel équilibre.

La tachycardie, les troubles vaso-moteurs, sudoraux, séborrhéiques, l'émotivité et les manifestations psychiques sont l'expression d'un déséquilibre neuro-végétatif à prédominance sympathicotonique.

L'état vagotonique des enfants, classiques depuis les recherches de Hess, Eppinger, Menssi, Glaser, n'est pas absolument constant et s'atténue progressivement. Tinel admet que vers la puberté se place très souvent une phase d'amphotonie avec prédominance alternée de tonus vagal et du tonus sympathique rythmée par le cycle cataménial. Danielopolu trouve, de 10 à 14 ans, 56 p. 100 de sympathicotoniques et de 14 à 16 ans, 100 p. 100. Guy Laroche, Melle Hirsch, Hadjipavlos, à l'aide de réflexes oculo-cardiaque et caeliaque enregistrés avec le polygraphe de Boulitte, trouvent chez 18 enfants de 10 à 16 ans, 3 cas d'amphotonie à prédominance sympathique et 7 cas de sympathicotonie pure.

On pourrait se demander si ces manifestations ne relèvent pas d'une névrose émotive constitutionnelle comme il en a été rapporté des cas par J. Decourt et le goitre pourrait, à la rigueur, être imputé à la même pathogénie.

Mais le caractère transitoire des phénomènes, la période où ils apparaissent, les symptômes qui les accompagnent et leur dis-

parition après la puberté permettent de les rattacher aux modifications hormonales qui se produisent à cette époque de la vie et de considérer ce syndrome comme neuro-endocrinien.

On ne peut parler d'hyperthyroïdie ni d'hypothyroïdie.

L'hyperthrophie thyroïdienne n'est que l'exagération d'un phénomène presque physiologique: l'augmentation du corps thyroïde, chez certaines femmes, lors de l'établissement des premières règles, à chaque période menstruelle, au moment de la grossesse et de l'accouchement.

Rien ne permet cependant d'affirmer l'hyperfolliculine. Les règles sont souvent précoces, trop abondantes et rapprochées, irrégulières (11 p. 100) ou absentes (31 p. 100) mais fréquemment normales. Les dosages de folliculine dans les urines nous ont toujours donné des chiffres inférieurs à 50 U. I. par litre. Le métabolisme basal pratiqué avant, pendant et après les règles ne paraît pas influencé par le cycle menstruel.

Un certain nombre d'arguments plaident en faveur du rôle joué par l'hypophyse, notamment la poussée de croissance concomitante portant essentiellement sur les membres, l'allongement des mains et des pieds, et de petits signes apanage de la première phase de la puberté, hyperpilosité, tendance à la séborrhée et à l'acné, hypersudation à odeur forte, développement exagéré des seins, hypersécrétion vaginale, apparition précoce, fréquence et abondance des règles.

L'exophtalmie elle-même peut être invoquée en faveur de cette hypothèse. Junkmann et Schöller, Loeser ont montré récemment que l'hormone thyroïdienne de l'hypophyse provoque l'exophtalmie d'une façon indépendante du sympathique, puisque cette action persiste après l'inhibition fonctionnelle par l'ergotamine et l'yohimbine et même la section chirurgicale; elle est indépendante de la glande thyroïde puisqu'elle persiste après l'ablation de celle-ci. On tend à considérer l'exophtalmie comme l'aboutissant d'un jeu complexe d'influences hormonales et nerveuses qui proviennent de l'hypophyse.

Nous avons cherché à mettre en évidence un excès d'hormone thyroïdienne par l'épreuve d'Arhon, mais celle-ci est d'interprétation délicate et de valeur discutée. Dans les quelques cas où elle a été pratiquée, elle a toujours paru négative ou douteuse.

Les dosages de gonadostimuline dans les urines, d'hormone mâle et de folliculine nous ont donné des chiffres normaux.

En tous cas, il s'agit de troubles purement fonctionnels, d'un déséquilibre momentané et il faut se garder de toute thérapeutique intempestive.

Bien entendu l'intervention chirurgicale et la radiothérapie sont contre-indiquées. Malgré l'abaissement du métabolisme basal, il faut s'abstenir de toute opothérapie thyroïdienne. L'iode elle-même ne doit être maniée qu'avec prudence et l'on doit s'en tenir à des doses très faibles qui ont une action plutôt favorable.

Le traitement hygiéno-diététique, avec quelques sédatifs neuro-végétatifs tels que le cratoégus, la passiflore, la valériane, la ballote, le saule blanc, l'anémone et, au besoin, des doses réfractées de phényléthylmalonylurée, suffit en général.

Dans quelques cas, l'action freinatrice sur l'hypophyse de l'hormone sexuelle antagoniste nous a paru provoquer une amélioration rapide.

Résumé.

A la puberté, dans la grande majorité des cas chez les filles. (29 F. 2 G.) une hypertrophie de la glande thyroïde avec tachycardie, troubles vaso-moteurs et psychiques, parfois légère exophtalmie et tremblements, pourraient en imposer pour une maladie de Basedow; mais ce syndrome en diffère par l'absence de signes de toxicité et par un abaissement paradoxal du métabolisme de base qui atteint fréquemment 30 %. Il ne s'agit pas non plus de goîtres endémiques: minces, de taille au-dessus de la normale, ces sujets ont une grande vivacité intellectuelle et motrice.

Son caractère transitoire, l'âge où il apparaît, le complexe endocrinien qui l'accompagne, distingue ce syndrome des manifestations parabasedowiennes et du syndrome sympathique basedowiforme. Il disparaît dès que les modifications physiques et physiologiques de la puberté ont achevé leur cycle et doit être attribué à un déséquilibre neuroendocrinien dans lequel l'hypophyse semble jouer le rôle principal, comme le montrent la poussée exagérée de croissance, le développement des caractères sexuels secondaires, l'hyperpilosité et d'autres petits signes.

Sur une variété de nanisme avec troubles particuliers du métabolisme de l'eau (syndrome oligodipsique avec hydrophilie).

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En 1938¹, nous avons attiré l'attention sur un trouble spécial du métabolisme hydrique, caractérisé par:

- 1° L'oligodipsie avec oligurie;
- 2° La densité élevée et permanente des urines;
- 3° L'hydrophilie de l'organisme, démontrée par l'absence de réponse polyurique et la rétention de la presque totalité de l'eau ingérée pendant l'épreuve de polyurie expérimentale d'Albarran-Volhard.

Ce syndrome oligodipsique avec oligurie et hydrophilie a été découvert chez un enfant de treize ans, atteint de nanisme avec, hypotrophie des organes génitaux.

L'étude de deux nouveaux faits comparables au précédent nous incite à grouper les éléments communs de ces trois observations pour individualiser ce type clinique et biologique.

Observation I. — Gal . . . (Jacques), treize ans, nous est adressé par le Dr Robert Broca.

Antécédents personnels. — Enfant né à terme, ne pesant que 2 kilogr. 040. Accouchement dystocique par bassin rétréci avec présentation de l'épaule et procidence du cordon ayant nécessité une version podalique et une application de forceps. Depuis sa naissance jusqu'à dix-huit mois, l'enfant fut nourri au sein et sa croissance parut facile: quoique petit, il semblait avoir récupéré une partie de son retard pondéral. Mais les parents ne peuvent fournir de chiffres précis quant à la taille et au poids.

A dix-huit mois, affection pulmonaire aiguë, mais sans gravité, qualifiée de bronchopneumonie, avec guérison assez rapide. C'est à ce moment que les parents remarquent la médiocre croissance de leur enfant; il prend peu de poids et commence à différer nettement des autres enfants.

¹ Debré (Robert) et Marie (Julien) Nanisme avec hypotrophie des organes génitaux Oligodipsie et hyperhydrophilie, Bull. et Mem. de la Soc. méd. Hôp. de Paris 8/7 1938. N° 25.

De dix-huit mois à neuf ans, on ne relève aucun épisode pathologique important. Seuls, quelques troubles fonctionnels sont signalés par les parents: anorexie, céphalée, vomissements assez fréquents, et, surtout fatigabilité rapide. Par contre, le développement psychique est normal. L'intelligence est vive malgré le retard scolaire: en effet, les parents, par prudence, évitent d'envoyer l'enfant à l'école.

A l'âge de neuf ans, le malade aurait présenté un second épisode pulmonaire aigu, qualifié encore de broncho-pneumonie et ayant nécessité un repos d'un mois au lit.

Enfin, en décembre 1937, l'enfant se plaint de douleurs abdominales, accompagnées de vomissements, ayant fait porter le diagnostic d'appendicite chronique.

Signalons encore que l'enfant se plaint souvent des jambes, surtout de la jambe droite, et qu'il a présenté à diverses reprises une tuméfaction brusque et douloureuse de la bourse droite. Nous avons pu assister une fois à ces manifestations, que nous avons rapportées à une torsion passagère de l'hydatide pédiculée de Morgagni.

Antécédents héréditaires. — *Père*: De développement normal. Taille 1.69 m. Présente des troubles hépatiques, liés à l'alcoolisme. Pas de malformation du squelette, en dehors d'une dépression sternale.

Mère: Taille 1.60 m, présente un bassin rétréci qui explique la difficulté de l'accouchement de Jacques et fit pratiquer une césarienne à la naissance du second enfant. Ce dernier est une fille âgée actuellement de huit ans et demi, dont le développement est normal et dont la taille dépasse déjà celle de son frère, de cinq ans son aîné.

Examen le 17 décembre 1937: l'enfant, âgé de treize ans, frappe immédiatement par le retard considérable de son développement corporel: il mesure 1.15 m, pèse 20.200 kg, c'est à dire le poids et la taille d'un enfant de sept à huit ans. Il présente donc cinq ans de retard sur les enfants du même âge. Cet état mérite donc d'être qualifié de nanisme.

Ce nanisme remarquable par le retard considérable du développement des organes sexuels. La verge est minuscule, comme celle d'un nourrisson; les testicules sont en place dans les bourses, mais petits et durs. A part cet état rudimentaire des organes génitaux, l'aspect morphologique de l'enfant est normal. Son nanisme est harmonieux, et les proportions entre le volume de la tête, la longueur du tronc et celles des membres sont normales. Lorsqu'on le compare, côte à côte, à un enfant de six ans, rien ne choque dans le morphologie de notre malade, en dehors de l'aspect des organes sexuels. Signalons cependant l'aspect triangulaire de la face avec le fort développement du front, réalisant l'aspect cranio-facial du type cérébral hippocratique, l'examen clinique minutieux permet de signaler encore quelques petites anomalies: l'enfant est brachycéphale, avec une légère plagiocéphalie, la bosse frontale gauche étant plus développée que la droite, et au contraire le pariétal droit plus bombé que le gauche. Le



Fig. 1. Jacques G. âgé de 13 ans (Obs. I); à côté de lui, à sa droite, un enfant normal de 6 ans.

maxillaire inférieur est petit, le menton pointu, mais sans rétrognathisme. On constate un retard notable de l'éruption dentaire, dont notre collègue Ruppe a bien voulu préciser les caractères. La première incisive permanente n'est apparue qu'à neuf ans. Actuellement il existe, à la denture inférieure, quatre incisives permanentes. Les canines et les molaires de lait persistent, encore bien implantées. Les premières molaires (dents de six ans) sont normales. Les dents de douze ans n'apparaissent pas. A la denture supérieure, les incisives centrales sont légèrement convergentes. Les incisives latérales évoluent seulement et sont obliques en bas et en dedans. Il persiste les canines et les molaires de lait. Les dents de six ans sont normales. Derrière la dent de six ans, l'arc alvéolaire ne s'est pas encore développé pour donner place à la dent de douze ans. Il n'existe pas d'anomalies de structure dentaire. Le palais est normal. Les incisives

inférieures sont en régression. Il n'existe aucun signe de rachitisme ni aucune déformation squelettique du rachis et des membres. On note au niveau du tégument du front un noevus paramédian gauche, en bande verticale, dont la teinte plus foncée disparaît à la pression. Quelques taches pigmentaires siègent au niveau du dos et sous le mamelon gauche.

L'examen du tube digestif révèle une sensibilité certaine de la fosse iliaque droite, mais sans point douloureux très localisé. L'examen viscéral est négatif: coeur, poumons, foie, rate, sont normaux. Le poulx bat à 60. La tension artérielle est de 9—5/5. La cutiréaction est négative. L'examen neurologique ne révèle aucun signe d'accompagnement, en particulier aucun trouble oculaire. Nous avons déjà signalé que l'intelligence de l'enfant était vive. Les radiographies du squelette sont normales. En particulier, les dimensions de la selle turcique sont normales, et on ne distingue pas de concrétions suprasellaires, comme dans les tumeurs de la poche de Rathke. Les cartilages de conjugaison ne sont pas encore soudés.

Examens complémentaires. — a) Urines. Ne renferment ni sucre, ni albumine. Cytologie normale.

b) Hémogramme du 13 Décembre 1937.

Hématies 4 425 000; Hémoglobine, 70 p. 100; Leucocytes, 7 500; Polynucléaires neutrophiles, 49; Polynucléaires éosinophiles, 9; Polynucléaires basophiles, 2; Moyens mononucléaires, 36; Lymphocytes, 4.

c) Epreuve d'hyperglycémie après ingestion de 30 grammes de glucose pur.

9 h.	Glycémie à jeun	0.84	} Pas de glycosurie pendant l'épreuve.
9 h. 40	Glycémie 30 minutes	1	
10 h. 10	Glycémie 60 minutes	1.13	
10 h. 55	Glycémie 105 minutes	1.00	
12 h.	Glycémie 165 minutes	1.80	

d) Examens chimiques du sang.

1° Urée sanguine:

le 20 Décembre 1937	0.43 gr p. 1 000
le 4 Janvier 1938	0.40 gr —
le 18 Janvier 1938	0.25 gr —

2° Acide urique sérique: 0 gr 028 p. 1 000 le 18 Janvier 1938.

3° Etude des chlorures sanguins:

Chlorures du sang, 3 janvier 1938:

Chlore globulaire	1.98
Chlore plasmatique	3.51
Rapport $\frac{C. G.}{C. P.}$	0.56

4° Examen chimique du sang du 31 Décembre 1937:

Lipides totaux.....	11.00 gr p. 1 000	
Cholestérine.....	2.10 gr	—
Phosphore.....	0.03 gr	—
Calcium.....	0.097 gr	—
Albumines totales.....	72.80 gr	—
Sérine.....	45.52 gr	—
Globuline.....	27.28 gr	—
Rapport $\frac{S}{G}$	1.66	—
Crée.....	0.51 gr	—

e) Ponction lombaire:

Leucocytes.....	2.6 par millimètre cube	
Albumine.....	0.22 p. 1 000	

f) Hormone gonadotrope urinaire (Dr Simonet):

9 Février 1938.....	Moins de 10 unités souris	
10 Février 1938.....	Moins de 20	— —
11 Février 1938.....	Moins de 10	— —

g) Examen oculaire (Dr Renard). Normal.

h) Métabolisme basal (Dr Goiffon) diminué de 13 p. 100 par rapport à un garçon de même âge.

L'hospitalisation du malade nous a permis de découvrir deux ordres de troubles insoupçonnés: l'un, intéressant la régulation thermique; l'autre, plus important, intéressant la régulation du métabolisme de l'eau.

I. Troubles de la régulation thermique. — Ils consistent essentiellement en hypothermie permanente, assez remarquable, puisque la température matinale est de 35°5 à 36°, et celle du soir de 36.2° à 37°. L'enfant n'accuse d'ailleurs aucun malaise, lié à cette hypothermie.

II. Troubles du métabolisme de l'eau. — Nous les avons découverts grâce à la pratique de l'épreuve de l'eau. Nous avons ainsi obtenu une courbe d'élimination de l'eau, pendant les dix premières heures de la journée, avec un véritable écrasement de la courbe pendant les premières heures, et une élimination lente et tardive dans la deuxième partie de la nuit, sous forme d'une seule miction abondante matutinale. A ce degré de netteté, nous n'avions jamais observé de trouble comparable chez l'enfant apyrétique. Nous avons alors entrepris une étude plus systématique du métabolisme hydrique du malade et nous avons constaté l'ensemble des faits suivants:

1° L'oligodipsie. L'enfant boit peu. Il se contente le plus souvent de 250 à 300 cc de boisson par jour. Pour réaliser l'épreuve de l'eau on doit lui faire ingérer, en une demi-heure 400 grammes de thé léger sucré. Nous avons éprouvé, à chaque épreuve, de grandes difficultés pour arriver à lui

faire ingérer cette quantité relativement abondante dans un laps de temps restreint. Parfois on a dû se contenter d'une ingestion de 350 grammes pour éviter le vomissement, qui aurait empêché de réaliser l'épreuve.

2° L'oligurie. Elle n'est également que relative. Le plus souvent, l'enfant urine de 250 à 500 cc. Le rythme des mictions est spécial et presque toujours le même. Voici le chiffres de quelques journées:

Le 12 Janvier 1938:

Première miction à 7 heures de.....	162 cc
Deuxième miction à 12 heures 15 de.....	14 —
Troisième miction à 13 h. 40 de.....	71 —
Total	247 cc

Le 13 Janvier:

Première miction à 5 h. 30 de.....	248 cc
Deuxième miction à 9 h. 20 de.....	74 —
Troisième miction à 10 h. 45 de.....	64 —
Total	356 cc

Le 14 Janvier:

Une seule miction à 9 h. 15 de.....	428 cc
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Le 15 Janvier:

Première miction à 6 heures de.....	350 cc
Deuxième miction à 13 heures de.....	180 —
Troisième miction à 14 heures de.....	28 —
Total	558 cc

Le 29 Janvier:

Première miction à 5 heures 45 de.....	220 cc
Deuxième miction à 9 heures 30 de.....	140 —
Troisième miction à 14 heures 15 de.....	62 —
Total	422 cc

Ainsi, le nombre des mictions est habituellement de trois par vingt quatre heures; l'enfant demeure sans uriner tout l'après-midi et presque toute la nuit, la miction la plus abondante étant évacuée au matin vers cinq ou six heures. Or, cette miction élimine la plus grande quantité de l'eau ingérée la veille, aux repas de midi et du soir. Cette étude du volume des urines démontre donc l'oligurie relative, le nombre restreint des mictions, et le retard de l'élimination des liquides, c'est à dire une opsiurie remarquable.

3° Résultats de l'épreuve de l'eau ou épreuve de diurèse expérimentale. Cette épreuve montre une rétention dans l'organisme pendant les quatre premières heures, des 9/10 de l'eau ingérée, et une élimination tardive avec débit horaire réduit, mais progressif. Pendant les quatre premières heures, l'enfant n'urine toutes les demi-heures que quelques centimètres cubes d'urine. Ainsi, lors de l'épreuve du 15 Février l'enfant

élimine à 8 h. 30 8 cc; à 9 heures, 4 cc; à 9 h. 30 3 cc; à 10 heures, 5 cc; à 10 h. 30 5 cc; à 11 heures, 3 cc; à 11 h. 30 0 cc; à 12 heures, 8 cc; soit pour les quatre premières heures un total de 36 cc. tandis qu'un enfant normal aurait éliminé au minimum 400 cc et dans certaines des mictions au moins 150 cc. Ainsi pendant les quatre premières heures, le malade n'a pas encore éliminé le 1/10^e de l'eau ingérée. L'enfant reçoit à midi et à 7 heures un repas sec. L'élimination se poursuit toujours sous de petits volumes, mais la quantité est cependant plus élevée, les mictions étant plus espacées: à 14 heures, 26 cc, à 16 heures, 26 cc; à 18 heures, 44 cc; enfin à 4 heures, 10 du matin, une grosse miction de 292 cc est évacuée et une dernière de 50 cc est émise à 7 heures, 30 du matin. L'enfant a éliminé dans les vingt-quatre heures 474 cc, mais suivant un rythme particulier. Le débit aqueux est donc de 10 cc en moyenne à l'heure pendant les quatre premières heures, de 15 cc en moyenne à l'heure pendant les six heures suivantes, de 30 cc dans les dix dernières heures. Ainsi l'épreuve de l'eau montre que le liquide ingéré est retenu dans l'organisme dans sa presque totalité pendant les quatre premières heures, puis les tissus — dans leur sens le plus général — abandonnent peu à peu l'eau emmagasinée, et avec un rythme de plus en plus accéléré pendant les heures nocturnes, pour aboutir à une abondante miction matinale.

4° Persistance de densités urinaires hautes et pouvoir concentrateur du rein élevé en permanence.

L'étude des densités des diverses mictions est également fort instructive. Elle montre l'absence de dilution, par suite de la faible élimination aqueuse. La densité la plus faible fut de 1 019 dans l'échantillon de 4 heures du matin; dans toutes les autres mictions, la densité fut toujours trouvée entre 1 024 et 1 029. Dans l'étude des autres courbes réalisées chez notre sujet, nous avons obtenu qu'une fois une densité de 1 015, lors de l'épreuve pratiquée après injection de thyroxine, par contre, nous avons obtenu des densités très hautes de 1 034, et après injection d'extrait post-hypophysaire, de 1 040. Pendant l'épreuve de l'eau, après injection d'extrait post-hypophysaire qui freine si notablement la diurèse pendant les quatre premières heures chez l'enfant normal, nous avons obtenu une élimination de 12 cc, l'abondante miction du matin fut de 312 cc et la totalité des urines émises en vingt-quatre heures de 434 cc. Sous le rapport volumétrique et rythmique, la quantité d'urine émise est identique à celle de l'épreuve ordinaire. Mais sous le rapport des densités, nous avons obtenu ce jour comme densité minima 1 021, et comme densité maxima 1 040. L'aspect des courbes, après épreuve simple et après injection d'extrait post-hypophysaire ou de thyroxine est d'ailleurs très comparable. Ainsi la densité urinaire révèle toujours des chiffres élevés. Après quelques jours de régime salé (régime sans sel + 10 grammes de sel) nous obtenons facilement un indice de concentration de 4 pour le NaCl, c'est à dire l'indice de concentration maxima. Sans chercher à obtenir la

concentration maxima pour l'urée, nous constatons, sans préparation, un indice de 80. Ainsi, la haute densimétrie urinaire correspond à une forte concentration des substances extractives dans l'urine en particulier NaCl et urée.

Observation II. — As... (Pierre), né le 19 mai 1922, vient consulter à la Clinique de l'Hôpital des Enfants-Malades le 26 Décembre 1940, pour un retard staturo-pondéral considérable. En effet, âgé de dix-neuf ans, ce garçon pèse 23.900 kg et mesure 1.18 m.

Antécédents. — Enfant né à terme, par le siège, pesant 4.300 kg et présentant deux malformations évidentes: un bec-de-lièvre et une ectopie testiculaire. Le bec-de-lièvre est opéré à l'âge de deux mois.

Pendant les deux premières années, la taille et le poids n'ont jamais été vérifiés, mais la mère affirme que la croissance de l'enfant était normale. Vers la troisième année, la mère s'aperçoit que l'enfant est anormalement petit et ne grandit pas.

Cette hypotrophie persiste les années suivantes, contrastant avec un développement intellectuels normal. A dix ans, pour la première fois, la taille est mesurée à l'école. Elle est de 0.90 m.

A treize ans, il reçoit une thérapeutique par extraits thyroïdien et hypophysaire. De treize ans à dix neuf ans, il grandit seulement de 28 centimètres.

Antécédents familiaux: — Mère bien portante, mesurant, 1.50 m ayant présenté 7 grossesses. La première fut normale. L'enfant est devenu un adulte de vingt-huit ans, bien portant et de taille normale (1.70 m). Ensuite se succédant 5 fausses couches, de deux à trois mois, spontanées, puis une septième grossesse, qui concerne le sujet faisant l'objet de cette étude.

Père mesurant 1.68 m, gendarme, mort accidentellement en 1936, quatre ans après la naissance de Pierre.

Examen du 26 Décembre 1940 — 1° Le nanisme est très marqué. La taille (1.18 m) et le poids (23.900 kg) sont ceux d'un enfant de neuf ans. Les formes sont de proportions normales, mais sans relief avec une adiposité légère diffuse. L'aspect de la face est disgracieux par suite de la cicatrice du bec-de-lièvre, de l'ensellure nasale et de l'écartement un peu exagéré des yeux. Le tour de tête mesure 53 centimètres. Le menton est petit sans rétrognathisme.

2° Le retard sexuel est considérable; non seulement les caractères sexuels secondaires sont absents, mais les organes génitaux sont hypotrophiques et comparables à ceux d'un nourrisson. Les testicules sont perçus dans les bourses, et sont du volume d'un gros haricot. La verge est très petite, d'une longueur de 2 centimètres environ. Une circoncision fut faite à l'âge de douze ans.

3° L'intelligence est normale, et ce garçon a franchi la première partie du baccalauréat.

4° La température est normale. La tension artérielle mesure en centimètres de mercure 9—6/5. Examen oculaire négatif, y compris le fond d'œil.

Examens complémentaires. — 1° Les radiographies révèlent un retard important de l'ossification, se traduisant par l'absence de soudure des cartilages dia-épiphyssaires de tous les os des membres. Les sinus frontaux ne sont pas développés. La selle turcique est normale.

2° Les fonctions rénales sont normales: urée sanguine, 0.35 gr p. 1 000; constante d'Ambar, 0.08; pas d'albuminurie; sédiment urinaire normal.

3° Métabolisme basal, 9.5 p. 100.

4° La réaction de Kahn est négative dans le sérum de la mère.

Hémogramme: Globules rouges, 4 320 000; Hémoglobine, 90 p. 100; Valeur globulaire, 1.04; Leucocytes, 11.700; Polynucléaires neutrophiles, 64; Polynucléaires éosinophiles, 2; Polynucléaire basophile, 1; Lymphocytes, 21; Grands Lymphocytes, 7; Monoocytes, 5.

6° Calcémie, 93 milligrammes pour 1 000.

7° Epreuves d'hyperglycémie:

a) Epreuve simple après l'ingestion de 20 grammes de glucose:

Glycémie à jeun.....	0.01 gr p. 1.000
Glycémie après 30 minutes.....	1.01 gr —
Glycémie après 60 minutes.....	0.90 gr —
Glycémie après 105 minutes.....	0.63 gr —
Glycémie après 165 minutes.....	0.58 gr —

b) Epreuve après ingestion de 20 Grammes de glucose et injection sous-cutanée d'extrait hypophysaire:

Glycémie à jeun.....	0.85 gr p. 1.000
Glycémie après 30 minutes.....	1.15 gr —
Glycémie après 60 minutes.....	1.20 gr —
Glycémie après 105 minutes.....	1.03 gr —
Glycémie après 165 minutes.....	0.90 gr —

Les deux courbes sont du type de l'insuffisance hypophysaire: petite flèche hyperglycémique, courte durée de la réaction hypoglycémie secondaire.

Les troubles du métabolisme de l'eau — Ce sont eux qui confèrent à cette observation un intérêt particulier. Ils se traduisent par:

a) L'oligodipsie. — Le sujet, d'une façon habituelle boit peu, et il lui est pénible d'absorber, en une demi-heure, les 500 cc nécessaires à la réalisation de l'épreuve d'Albarran-Volhard. Il lui fut même impossible d'absorber les 700 cc qui avaient été prescrits lors d'un examen pour

essayer de forcer la diurèse. L'oligurie est habituelle, aux environs d'un demi-litre.

b) L'hyperhydrophilie est mise en évidence par l'épreuve d'Albarran-Volhard. Voici les résultats d'une des nombreuses épreuves pratiquées. Le 19 Septembre 1941 le sujet ingère entre 7 heures 30 et 8 heures 500 cc de thé léger. Il élimine à 8 heures 32 cc; à 9 heures 14 cc; à 9 h. 30, 14 cc; à 10 heures, 12 cc; à 10 h. 30, 16 cc; à 11 heures, 20 cc; à 11 h. 30, 19 cc; à 12 heures 20 cc.

Ainsi, pendant les quatre premières heures de l'épreuve de dilution, le sujet n'a rejeté que 154 cc soit moins du tiers de l'eau ingérée. Après un repas, l'élimination se poursuit toujours sous de petits volumes, mais la quantité est cependant moins faible.

A 14 heures, 70 cc; à 16 heures, 62 cc; à 18 heures, 70 cc; à 20 heures, 95 cc; à 22 heures, 35 cc; à 8 heures, 36 cc.

La quantité totale d'eau éliminée en vingt-quatre heures est donc de 522 cc. Les courbes faites après injection d'extrait de lobe antérieur d'hypophyse, puis d'extrait cortico-surrénal sont identiques dans leurs traits essentiels.

Ainsi, nous retrouvons chez ce sujet le même trouble que celui que nous avons signalé en 1938. A savoir, l'absence de réponse polyurique à l'épreuve de l'eau et la rétention de la plus grande partie de l'eau ingérée pendant les quatre premières heures de l'épreuve d'Albarran-Volhard, les tissus abandonnant lentement et tardivement l'eau emmagasinée.

c) persistance de densités urinaires hautes et pouvoir concentrateur du rein élevé en permanence.

L'étude des densités montre que la densité la plus faible fut 1010, dans le seul échantillon de dix heures. Toutes les autres densités varient de 1018 à 1025, et d'autres jours, même pendant l'épreuve de dilution, des densités de 1030 furent obtenues.

Après régime fortement salé (10 grammes par jour) les 26, 27 et 28 Février 1941, la diurèse atteint 443 cc, 759 cc, 784 cc et le taux des chlorures urinaires se maintient à 16.96 gr, 14.96 gr et 14.56 gr p. 1 000 dans les urines de vingt-quatre heures.

Le 15 Janvier 1947, nous réexaminons le malade. Il est âgé de vingt-quatre ans et huit mois, mesure 123 centimètres et pèse 30 kilogramme. Sa morphologie générale et génitale est identique à celle constatée en décembre 1940.

En particulier, l'hypotrophie des organes génitaux ne s'est pas modifiée, et aucun caractère sexuel secondaire n'est apparu. Toutes les dents de lait sont finalement tombées, la dernière en 1944 (canine). Les dents de la deuxième dentition sont mal implantées, et la deuxième prémolaire droite s'est développée dans le palais. Aucune dent de sagesse n'est apparue. La voix est celle d'un enfant, avec résonnement par suite du bec-de-lièvre. Ce garçon a été au baccalauréat (2^e partie), après deux

ans de préparation. Il remplit les fonctions de rédacteur dans une compagnie d'assurances et son développement intellectuel est donc normal, mais moyen.

Les mensurations des divers segments du corps donnent les chiffres suivants:

Longueur de la main (interligne radiocarpien à l'extrémité du médus); 13 centimètres; longueur du buste, 42 centimètres, longueur des membres inférieurs (épine iliaque antéro-supérieure à la malléole externe) 64 centimètres; longueur du pied, 18 centimètres (pointure 33 pour les chaussures); tour du crâne 53 centimètres.

Observation III. — Dul . . . (Guy), né le 19 mars 1929, entre dans notre service de l'hôpital Hérold le 8 février 1944, sur les conseils de notre ami le Dr Robert Mallet, pour un retard de croissance. En effet âgé de quinze ans, il mesure 1.30 m, pèse 29.500 kg et il n'est apparu aucun signe de début de puberté.

Antécédents. — Né à terme, par le siège, poids de naissance inconnu; a semblé normal jusqu'à l'âge de trois ans. A cet âge, l'enfant a présenté une broncho-pneumonie de rougeole à la suite de laquelle son développement aurait été compromis. Ictère catarrhal. Cutiréaction négative. Parents bien portants, le père mesure 1.71 m. Réactions de Wassermann et de Kahn négatives chez le mère le 19 mai 1944. Soeur décédée de méningite (?) à l'âge de douze mois en 1927.

Examen clinique — Les deux constatations essentielles sont l'insuffisance de la taille et l'hypotrophie remarquable des organes génitaux.

1° Le nanisme — La taille mesure 1.30 m, le poids 29.500 kg. La morphologie de l'enfant est normale et les rapports entre les divers segments du corps paraissent proportionnels. Les mensurations segmentaires fournissent les chiffres suivants: Tronc, 0.66 m; membres inférieurs 0.68 m; longueur des pieds 0.21 m; longueur des mains (au médus), 0.15 m; membres supérieurs gauches 0.57 m; membre supérieur droit 0.55 m; tour de tête 53 centimètres.

L'ensemble du corps de cet enfant est comparable à celui d'un enfant de huit ans. La tête est normale, le menton petit, un peu triangulaire, alors que le crâne est bien développée. Les cheveux sont abondants, un peu secs: les cils nombreux, bien dessinés; les sourcils clairsemées, surtout au niveau de la queue.

Le pannicule adipeux est fourni, ébauchant un double menton modelant les formes particulièrement au niveau du tronc, où les seins sont gras. Au niveau des membres, la graisse de couverture est normale; les mains sont fines et potelées. La peau est fine partout. Au niveau des membres, elle est sèche et légèrement desquamante.

Le système pileux est complètement absent au niveau des régions pubienne et axillaire. Il n'existe que quelques rares poils à la face dorsale

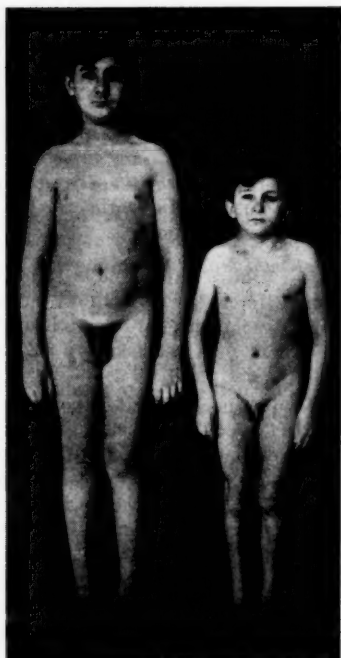


Fig. 2. Guy D. âgé de 15 ans (Obs. III) à droite; à côté de lui, un enfant normal de son âge.

de la partie supérieure des avants bras et un fin duvet au niveau des membres inférieurs.

De nombreux noevi pigmentaires et vasculaires sont disséminés sur les téguments. On en compte, en négligeant les éphélides, une vingtaine sur le dos, du diamètre d'une lentille à un pois. On constate une plage café au lait au niveau de la crête iliaque.

Les organes génitaux sont remarquables par l'insuffisance de leur développement: les deux testicules, qui peuvent être abaissés dans les bourses, sont du volume d'un petit haricot et l'ensemble, verge et testicules, correspond aux organes génitaux d'un enfant de trois ans.

La régulation thermique de cet enfant n'est pas absolument normale. En effet pendent la durée de son hospitalisation (trois mois), la température fut régulièrement mesurée cinq fois par jour: à 7 heures, 11 heures, 15 heures, 19 heures, 22 heures. Nous avons constaté, pendant une période

de onze jours, que la température de 22 heures ou de 7 heures était très basse: 35.6°, 35.5°, 35.4°.

L'examen des autres viscères (poumon, coeur, rate, foie, système nerveux) est normal. La tension artérielle mesure 10 centimètres de Hg pour la maxima et 7 pour la minima.

L'appareil oculaire est entièrement normal y compris le fond d'œil. Par contre, le système dentaire (25 Février 1944) présente un retard considérable pour l'âge de l'enfant. Au maxillaire supérieur gauche, la 2^{ème} molaire de lait, la canine et la 1^{ère} prémolaire n'ont pas encore fait leur éruption. Au maxillaire supérieur droit, la canine de lait, la lère et la 2^{ème} molaire de lait sont encore sur l'arcade. Au maxillaire inférieur gauche, les dents définitives existent; la dent de douze ans fait son éruption. Au maxillaire inférieur droit, la canine et la lère molaire n'ont pas encore fait leur éruption. Présence de la 2^{ème} molaire de lait. La dent de douze ans pousse. L'articulation des dents est normale.

Le développement intellectuel de l'enfant est sensiblement normal. Il répond correctement à 3 tests sur 5, d'adulte (méthode de Binet-Simon).

Les radiographies du squelette, en particulier de la selle turque, sont normales. On constate seulement un retard d'apparition du noyau oléocranien, au niveau des articulations du coude.

Examens de laboratoire:

1° Hémogramme: Hématies, 4 400 000; Hémoglobine, 80 p. 100; Valeur globulaire, 0.90; Leucocytes, 6 600; poly. neutrophiles, 41; Poly-éosinophiles, 13 p. 100; poly. basophiles, 1; Lymphocytes, 9. Grands et moyens lymphocytes, 28, Monocytes, 8.

2° Métabolisme basal, 41 (—4 p. 100).

3° Dosages sanguins: Urée, 0.35 gr p. 1 000; Glycémie à jeun, 0.85 gr; Chlore globulaire, 1.85 gr; Chlore plasmatique, 3.80 gr; Rapport érythro-plasmatique $\frac{\text{Cl. G.}}{\text{Cl. P.}} = 0.49$.

Epreuve d'hyperglycémie le 6 mai 1944, Glycémie à jeun, 1.10 gr. Après ingestion de 50 grammes de glucose et par dosage sur 0 cc. I de sang pris au doigt, sauf pour le dosage de 10 h. 45 où le sang fut prélevé par ponction de la veine du bras. Tous les dosages ont été effectués par la micro-méthode d'Hagedorn—Jansen.

8 h. 15.....	1 gr 10
8 h. 45.....	1 gr 57
9 h. 15.....	1 gr 62
9 h. 45.....	1 gr 86
10 h. 15.....	1 gr 68
10 h. 45.....	1 gr 06

A 10 h. 45 on prélève également par ponction de la veine 1 cc de sang pour doser la glycémie, à titre de comparaison par la méthode de Beaudoin

—Lévin, que nous considérons comme plus précise. Elle donne le chiffre de 0.88 gr p. 1 000 au lieu de 1.06 gr fourni par la méthode d'Hagedorn. Cette dernière semble donc donner des résultats plus élevés.

Etude biologique des mouvements de l'eau. — Nous l'avons poursuivie suivant nos techniques habituelles, par l'épreuve d'Albarran-Volhard. Nous nous sommes ainsi assurés de l'existence du trouble déjà constaté chez les deux autres sujets atteints du même syndrome, à savoir la rétention de l'eau pendant les quatre premières heures de l'épreuve. A la vérité, le trouble d'oligodipsie avec oligurie et hyperphrophilie est moins intense que chez nos précédents malades, mais il demeure indiscutable.

Nous avons ensuite varié les conditions de l'épreuve en la réalisant en régime chloruré et déchloruré et en cherchant à apprécier les modifications que pourrait apporter l'injection de divers extraits glandulaires.

1° Epreuve de l'eau du 23 Février 1944, en régime déchloruré. — L'enfant pesant 29.500 kg, ingère 600 cc de tilleul sucré entre 7 h. 30 et 8 heures. Il urine: à 8 heures, 20 cc; à 9 heures, 8 cc; à 9 h. 30, 12 cc; à 10 heures, 10 cc; à 10 h. 30, 5 cc; à 11 heures, 10 cc; à 11 h. 30, 7 cc; à 12 heures, 9 cc. L'enfant a donc rejeté pendant les quatre premières heures 101 cc seulement sur les 600 cc ingérés. Les 5/6 de l'eau ingérée ont donc été retenus dans l'organisme. Dans les mictions de la matinée, la densité urinaire est demeurée entre 1.020 et 1.027. L'Hydrémie mesurée avant l'épreuve était de 81, 5 p. 10. On constate une légère augmentation de l'Hydrémie à 8 h. 30 (83.2 p. 100) et à 9 h. 30 (83.9 p. 100); à midi, elle est presque revenue à son taux initial; 82 p. 100.

Dans l'après midi la diurèse devient plus active; l'enfant élimine 180 cc à 16 heures; 260 cc à 18 heures; 345 cc à 20 heures et 525 cc à 8 heures le lendemain. La chute de poids est de 250 grammes en vingt-quatre heures, soit 8 grammes par kilogramme. La densité la plus faible fut constatée à 20 heures (1.007); la diurèse totale des vingt-quatre heures fut de 1.400 cc.

Nous constatons donc, dans ce cas, les caractères essentiels révélés par l'épreuve de l'eau au cours du syndrome oligodipsique avec hyperphrophilie, à savoir l'absence de réponse polyurique à l'épreuve de l'eau, la rétention de la plus grande partie de l'eau ingérée, la persistance de fortes densités urinaires.

Nous avons répété cette épreuve onze fois, en faisant varier les conditions de sa réalisation.

2° Epreuve de l'eau en période de régime chloruré du 30 mars 1944. — Ingestion de 600 cc, il rejette: à 8 heures, 25 cc, à 8 h. 30, 15 cc. à 9 heures, 20 cc, à 9 h. 30, 20 cc, à 10 heures, 10 cc, à 10 heures 30, 15 cc, à 11 heures, 10 cc, à 11 h. 30, 20 cc, à 12 heures, 10 cc, soit pour les quatre premières heures: 145 cc. Pour les vingt-quatre heures, la diurèse totale fut 930 cc.

TABLEAU.

Nature des épreuves	Vol. des 4 1ères h.	Vol. des 24 h.	Densité maxima	Densité minima	Variation du poids
Régime chlorure					
Epreuve de l'eau simple	145 cc.	930 cc.	1028 à 14 h.	1010 à 18 h.	+ 50 gr
Epreuve avec injec. d'extrait hypophysaire total	135 cc.	945 cc.	1028 à 11 h.	1004 à 16 h.	+ 100 gr
Epreuve avec extrait posthypophysaire	136 cc.	808 cc.	1022 à 8 h. 30	1012 à 16 h.	- 400 gr
Epreuve avec thyroxine	230 cc.	840 cc.	1021 à 9 h. 30	1012 à 16 h.	- 400 gr
Epreuve avec désoxy- corticostérone	172 cc.	722 cc.	1027 à 18 h.	1012 à 12 h.	- 150 gr
Régime déchlorure					
Epreuve de l'eau simple	101 cc.	1425 cc.	1027 à 11 h.	1007 à 20 h.	- 250 gr
Epreuve avec injec. d'extrait hypophysaire total	74 cc.	821 cc.	1031 à 9 h. 30	1006 à 18 h.	- 350 gr
Epreuve avec extrait posthypophysaire	89 cc.	1209 cc.	1031 à 10 h. 30	1007 à 20 h.	- 700 gr
Epreuve avec thyroxine	98 cc.	1106 cc.	1027 à 8 h.	1008 à 18 h.	- 150 gr
Epreuve avec désoxy- corticostérone	79 cc.	472 cc.	1025 à 11 h. 30	1004 à 18 h.	- 150 gr

3° Les autres épreuves furent étudiées en régime chloruré et en régime déchloruré, en injectant au début de l'épreuve divers extraits glandulaires (extrait hypophysaire total, extrait de post-hypophyse, thyroxine, désoxycorticostérone), nous n'avons pas constaté de modifications appréciables de la courbe de l'eau sous l'influence de ces diverses substances. Le seul fait positif et constamment retrouvé est une diurèse totale des quatre premières heures de l'épreuve, toujours plus faible en régime déchloruré qu'en régime chloruré.

Ces trois observations superposables des points de vue clinique et biologique vont permettre d'individualiser les traits essentiels du syndrome.

Du point de vue somatique et psychique, les trois sujets sont comparables:

- 1° Nanisme très marqué mais proportionné.
- 2° Hypotrophie considérable des organes génitaux avec absence totale de puberté.
- 3° Facies juvénile à traits fins, avec face petite et menton d'aspect triangulaire.
- 4° Pannicule adipeux bien développé sur le thorax avec seins graisseux, modelant les formes, réalisant un aspect féminin, avec une peau fine et douce.
- 5° Retard d'apparition de certains points d'ossification; intégrité dans les 3 cas de la selle turcique dont les contours et les dimensions demeurent normaux.
- 6° Retard souvent considérable de l'évolution dentaire.
- 7° Hypothermie, soit habituelle soit par période.
- 8° Intelligence normale sans être brillante.

Cet ensemble rappelle, dans la plupart de ses traits, le nanisme hypophysaire de Souques, et c'est bien à ce type clinique que nous rattachons nos trois malades. Nous apportons en faveur de cette thèse, un argument biologique de valeur: les modifications de la courbe d'hyperglycémie provoquée qui, chez deux des sujets (obs. I et II) réalise la variété classiquement attribuée à l'insuffisance du lobe antérieur de l'hypophyse; hypoglycémie initiale, écrasement de la courbe par suite de la petitesse de la flèche hyperglycémique.

Du point de vue biologique, l'originalité de nos observations porte sur l'étude du métabolisme de l'eau qui montre dans les trois cas une perturbation identique, dont les éléments essentiels sont:

- 1° L'oligodipsie bien mise en évidence lorsqu'il est, demandé au sujet d'ingérer rapidement un volume d'eau important comme dans la réalisation de l'épreuve de l'eau d'Albarran-Volhard.
- 2° L'oligurie, relative, les volumes urinaires des vingt-quatre heures demeurant régulièrement faibles.
- 3° L'absence de réaction polyurique à l'épreuve de diurèse provoquée. De tous les caractères dont la composante illustre le trouble du métabolisme de l'eau chez ces sujets, ce dernier apparaît le plus important. Il est facile à dévoiler grâce à l'épreuve de

l'eau; il est très explicite par sa netteté puisque l'élimination hydrique est considérablement diminuée, et que parfois le 1/10 seulement de l'eau ingérée est rejeté; enfin il est remarquable par sa constance: nous avons maintes fois répété l'épreuve chez chacun de ces enfants, particulièrement dans l'observation III, jamais nous n'avons réussi à modifier la texture de la courbe d'eau et jamais, même en nous aidant d'injections d'hormones nous n'avons obtenu une courbe se rapprochant du type normal.

4° La persistance de densités urinaires hautes avec permanence de l'élévation du pouvoir concentrateur du rein. Les densités urinaires des mictions recueillies pendant les quatre premières heures de l'épreuve correspondant à l'épreuve de dilution sont toujours élevées, au-dessous de 1015. Dans une ou deux mictions de l'après-midi, on constate des densités plus faibles, parfois même 1005, mais nous n'avons jamais obtenu chez aucun de ces sujets une densité de 1 001 ou de 1 002, comme il est habituel chez le sujet normal.

Un dernier caractère unit ces trois observations: l'impossibilité de modifier le syndrome clinique et biologique avec les extraits glandulaires dont nous disposons actuellement. Les hormones hypophysaires (gonadotrope et somatotrope), les extraits de lobe antérieurs d'hypophyse, l'hormone testiculaire, l'extrait thyroïdien, furent sans action sur le syndrome clinique. Quant au syndrome hydrophilique avec absence de réponse polyurique nous avons déjà indiqué sa constance et son irréversibilité quelle que soit l'hormone injectée avant l'épreuve de l'eau.

L'explication du syndrome clinique doit être cherchée, pensons-nous, dans une insuffisance du fonctionnement du lobe antérieur de l'hypophyse. L'altération fonctionnelle ou lésionnelle de ce lobe est-elle primitive? Ne serait-elle pas la conséquence d'une lésion acquise ou congénitale de la région infundibulotubérienne? Nous ne pouvons répondre avec certitude, en l'absence de documents anatomiques. Sans doute, la forme de la selle turcique est normale sur les différents films, mais cet aspect n'implique pas l'intégrité de la glande. L'absence d'infection en particulier de syphilis congénitale ne plaide pas pour le rôle de ce facteur étiolo-

logique. L'absence de signes cliniques et radiologiques d'hypertension intracrânienne permet de rejeter une néoformation de la région hypophyso-tubérienne, en particulier le cranio-pharyngiome. Il est possible que l'altération neuro-hypophysaire soit malformative et congénitale. Dans nos 3 cas des malformations associées ont été notées; le premier enfant présentait un noeuveau frontala médian; le second un bec-de-lièvre et une ectopie testiculaire; le troisième de nombreux naevi pigmentaires et vasculaires de la face et du dos.

Le trouble de la régulation hydrique avec oligodipsie, hydrophilie, et absence de réaction polyurique à l'épreuve de diurèse provoquée peut-être expliquée soit par un hyperfonctionnement du lobe postérieur, soit par une insuffisance du lobe antérieur. L'excès de sécrétion de l'hormone antidiurétique posthypophysaire est peu vraisemblable. Cette sécrétion serait la seule exagérée, les autres hormones sécrétées par ce lobe, en particulier l'hormone pressive, n'étant pas en excès, comme le montrent les chiffres normaux de la tension artérielle constatés chez nos enfants. Nous pensons qu'il est plus satisfaisant d'incriminer l'atteinte du lobe antérieur lui-même. Certains endocrinologistes ont avancé que le lobe antérieur de l'hypophyse sécrétait une hormone polyurique et que l'intégrité de ce lobe était indispensable pour réaliser le diabète insipide. La logique tend à rattacher le trouble du métabolisme de l'eau constaté dans nos trois observations à la même cause déterminant tous les autres éléments du syndrome, c'est-à-dire la suppression des fonctions essentielles attribuées au lobe antérieur de l'hypophyse et principalement la croissance staturale, le développement des organes génitaux et de la crise pubertaire, l'écrasement de la courbe d'hyperglycémie.

Growth and Maturity of Boys in Relation to School-Leaving Age.

By **Richard W. B. Ellis**, Edinburgh, Scotland.

The present study was undertaken as the result of an investigation of the growth of Belgian children during the period of nutritional deprivation associated with the German occupation (Ellis,

1945). Growth curves constructed from the medical records of schoolchildren and boys in Government employment suggested that insufficient diet might have resulted in a delay in the average age of onset of puberty. Whilst it was possible to get some confirmation of this from the menstrual histories of older girls, it was found that in the case of boys no pre-war figures were available from which a normal distribution curve of age-onset of puberty could be constructed, nor were any particulars given of the state of maturity of individual boys in the records of their medical examinations.

It was felt, therefore that since routine medical records of boys in Great Britain are equally deficient in this respect, it would be worth testing whether a simple clinical method of maturity-grading, such as could be applied in routine examinations, would yield significant information in relation to growth and could form the basis for constructing a normal distribution-curve of age-onset of puberty in controlled groups.

The criteria employed in maturity-grading have been described in more detail elsewhere (Ellis, 1946), and were found subsequently to approximate to those suggested by Greulich and his co-workers (1942). In the present study, however, only three maturity-grades were recognised instead of Greulich's five. The most immature group, to which the description of pre-pubescent was originally given but for which the term non-pubescent is now preferred in order to avoid confusion with the nomenclature of other authors, consisted of those boys in which pigmented terminal hair in the pubic and axillary areas was entirely absent, and genital development was infantile or minimal. The second or pubescent group included those in whom pigmented terminal hair was present even in minimal amount and/or development of penis or testicles was clearly recognizable by increased length of the penis without corresponding development of the corpora cavernosa, and of the testicles by peripheral widening of the scrotum, softening of the body of the testis, and relative increase in size of the testis to the epididymis. The grading «adolescent» was given to boys showing the presence of terminal hair plus development of the corpora cavernosa plus well-marked development of the body of the testis.

In addition, in each examination distribution of pubic and axillary hair if present was recorded as P1 to P5 and A1 to A3; and the presence or absence of comedones and gynaecomastia noted. (Gynaecomastia was observed in none of the non-pubescent boys, in 12.9 per cent of the pubescent, and in 32.1 per cent of the adolescent). Rugosity of the scrotum and pitch of the voice were found to be too variable to be of much value, though an obviously »broken» voice was taken as confirmatory evidence of adolescence.

It is obvious that such a classification cannot be rigid and that borderline cases will be seen in which decisions as to grading will be somewhat arbitrary. It can also be objected that the non-pubescent and adolescent groups are not homogeneous; the former contains boys who are completely immature and those within a few months of manifest pubescence, whilst the latter (adolescent) group includes boys in early adolescence and also those in whom growth has practically been completed. Within these limitations, however, the system of maturity-grading described does, from the data to be presented, appear to provide a basis for recognizing three successive stages of maturity, and a means of comparing the growth and physical performance of boys of the same age but of different grades of maturity.

The clinical material for study was derived from two large orphan-schools in England and two residential homes for working boys in Edinburgh, and consisted of boys aged 9 to 18 in good general health. Those who had had prolonged or recent illness likely to have affected their growth or development were excluded, as were those showing cryptorchidism. No cases of other endocrine disorder or pathological obesity were encountered. Boys over 18 were not included, as those available had been excluded from military service for various reasons including poor general physique, and were not therefore representative.

On the results of 662 examinations, the following figures (Table 1 and fig. 1) show the percentage of boys graded as non-pubescent, pubescent, and adolescent in each year-age group. The percentage of non-adolescent boys i. e. 100 minus percentage of adolescents in each year-age group is also given in Table 1 and fig. 3.

It will be seen that the percentage of non-pubescent boys falls

TABLE 1. Maturity grading of boys aged 9 to 18 (662 Examinations).

Age (years)	Number	Non-pubescent (per cent.)	Pubescent (per cent.)	Adolescent (per cent.)	Non-Adolescent (per cent.)
9-10	52	100	0	0	100
10-11	40	95	5	0	100
11-12	74	86.5	13.5	0	100
12-13	95	64.2	35.8	0	100
13-14	135	47.4	43.7	8.9	91.1
14-15	120	12.5	39.2	48.3	51.7
15-16	78	1.3	29.5	69.2	30.8
16-17	33	6.1	18.2	75.7	24.3
17-18	35	0	11.4	88.6	11.4

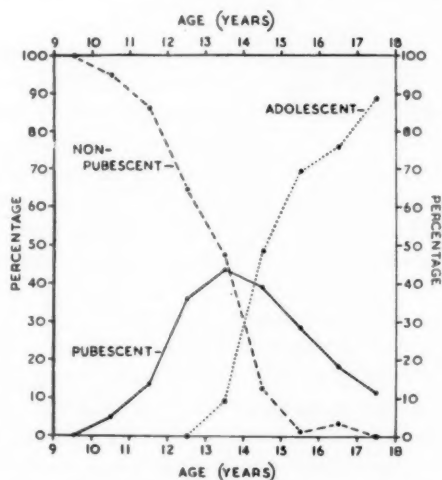


Fig. 1. Percentages of non-pubescent, pubescent, and adolescent boys in each year-age group (662 examinations).

from 100 in the 9 year-old group to 0 in the 17 year-old group, whilst the percentage of adolescents rises from 0 in the 12 year-old group to 88.6 in the 17 year-old group. The distribution curve of pubescent boys shows a peak between 13 and 14 years (at which age the division into non-pubescent and pubescent boys is most

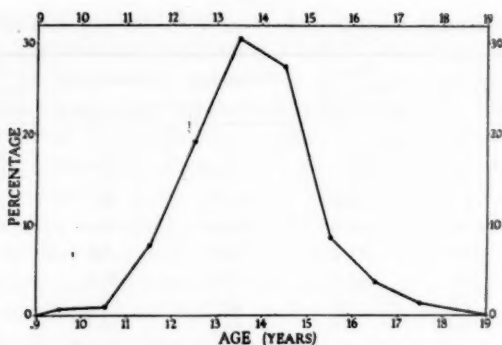


Fig. 2. Percentage of 470 girls showing onset of menstruation in each year of age (Ellis, 1947).

even). That the curve is slightly more spread in the higher than the lower age groups is possibly related to the fact that the 16 to 18 year-old boys were almost entirely derived from the residential homes for working boys and that their earlier nurture had been in most cases less good than that of boys in the two orphan schools. The results, however, are more nearly lognormal (i. e. in this instance the log of the age rather than the age itself is normally distributed) as occurs in many biological measurements (Gaddum 1945).

Fig. 1 illustrates clearly the effect that the raising of the school leaving age from 14 to 15 will have on the maturity of boys seeking employment. Thus at 14 there are as many non-pubescent boys as adolescents, and approximately 40 per cent of the total are pubescent. At the age of 15, nearly 60 per cent of the boys are adolescent and less than 10 per cent non-pubescent. This obviously has a practical bearing on conditions of juvenile employment, which will be referred to subsequently.

Comparing the distribution-curve of pubescence in boys with the distribution curve of age-onset of menstruation in girls (Ellis, 1947), it will be seen that the two are similar and that both show a peak between 13 and 14 years.

Since the stage of development described as pubescence in boys represents an earlier stage of maturity than does menstruation

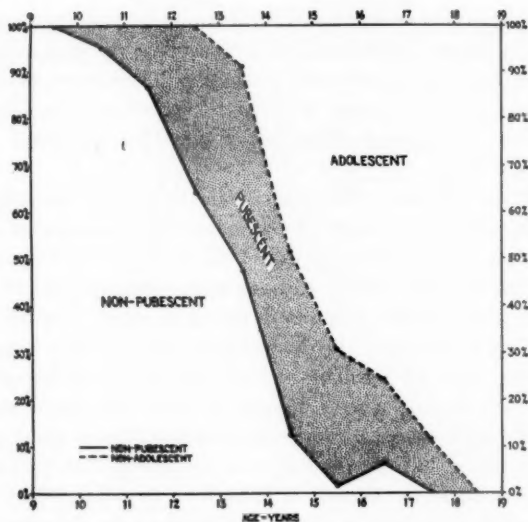


Fig. 3. Distribution of pubescence as shown by percentage of boys non-pubescent and percentage non-adolescent in each year of age (from Table 1).

in girls and corresponds rather to the appearance of breast development and pubic hair which may precede menstruation by 12 or more months, this is consistent with the observation that maturity normally occurs earlier in girls than boys.

Duration of Pubescence. If the data given in Table 1 is replotted (fig. 3) to show the percentage of boys non-pubescent and the percentage non-adolescent in each year of age, the curves suggest that the duration of pubescence is longer in boys maturing early and late than in those maturing at the mean age.

The average duration of pubescence as indicated by fig. 3 would be approximately:

Age at Onset (years)	Duration of pubescence (years)
10.5	2.5
11.5	2.2
12.5	1.7
13.5	1.2
14.5	2.4
15.5	? 3 (curve incomplete)

In order to check this clinically, it would be necessary to make serial examinations of the same boys from the stage of non-puberty to adolescence, and whilst such a study would have to be carried out over a number of years, it is one for which routine maturity-grading on school and industrial medical examination would provide the data.

Height and Weight. Using the maturity-grading described, an initial comparison was made of the mean height and mean weight of boys of the same year of age but of different degrees of maturity, with the result that within the age range studied viz. 12 to 16 years the more mature boys were found in every instance to be heavier and taller than the less mature boys of the same age. These boys were all resident in the two schools (referred to as School A and B) and since comparisons were only made between boys in the same schools, each group had been living under similar environment and on the same diet as the group with which comparison was made for periods of from 3 to 10 years. Each group comprised 12 to 25 boys, with the exception of the pubescent 15—16 year-old group which included 8 only.

The differences in each instance between the mean heights and weights of boys of similar age but in different maturity groups were substantial, and although all the groups were relatively small, it was considered that the experimental conditions were sufficiently well controlled and the probability of error in each instance sufficiently low to render the results significant (Ellis, 1946).

In order to determine at how early an age these differences were apparent, mean height and weight curves were constructed for each maturity-age group, and those for boys of the same age and school compared. School A was particularly suitable for a retrospective analysis of this type, as all the boys entered at the age of five, and were weighed and measured by trained personnel on entry and annually thereafter. Until 1945, all had remained at school throughout the year, so that any variations in diet during the war years would affect all boys of the same age equally. In School B. the records were equally reliable, but boys entered at varying ages, from 8 years onwards, and returned home for the

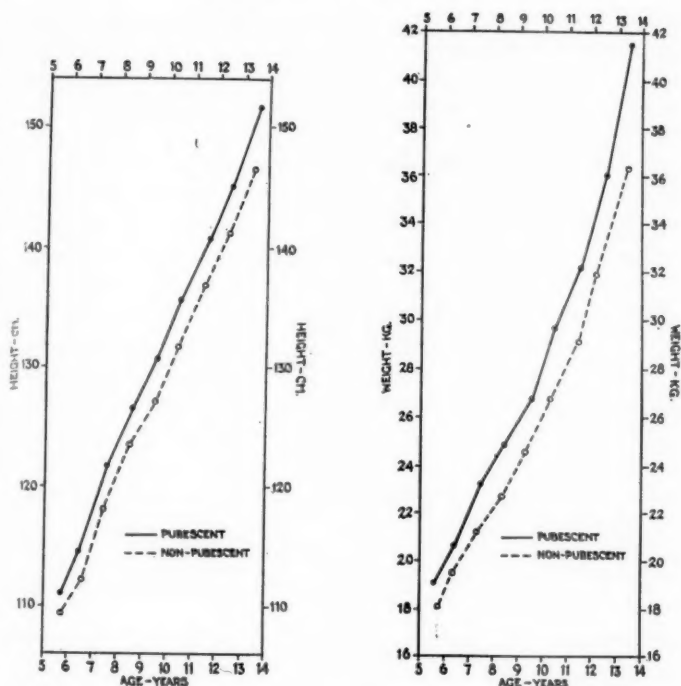


Fig. 4 and 5. Growth curves of boys aged 13—14 years at time of grading into non-pubescent and pubescent.

holidays. It was found that whilst the curves tended to diverge with increasing maturity, the groups of earlier-maturing boys were in all instances heavier and taller than their later maturing contemporaries to the earliest age for which measurements were available, i. e. in the case of School A, the sixth year of age.

Figs. 4 and 5 illustrate the growth curves of boys who were aged 13—14 at the time of grading, and shows the comparison between the pubescent and non-pubescent groups (School A).

Figs. 6 and 7 show a similar comparison between the growth curves of boys pubescent and adolescent when examined at the age of 15 to 16 (School B).

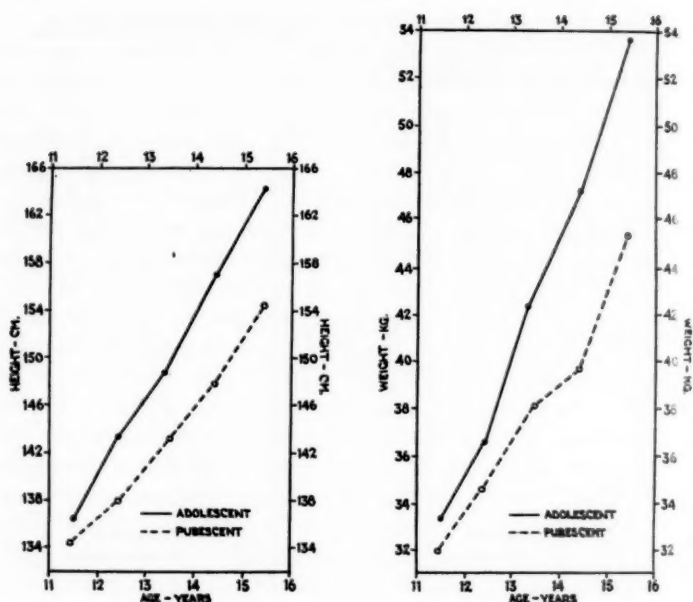


Fig. 6 and 7. Growth curves of boys aged 15—16 years at time of grading into pubescent and adolescent.

Since the occurrence of early or late maturity is likely to be multifactorial, it cannot of course be argued from these mean values that a small child will necessarily mature and a large child early; the curves do, however, suggest that groups of earlier and later maturing boys may show differences in mean height and weight which are demonstrable long before the earliest manifestations of puberty are present.

Hip circumference. It was noted clinically in the course of the examinations that the onset of puberty was in many cases associated with some degree of fat-deposition in the pelvic region and with muscular development, particularly of the buttocks. It was therefore decided to measure the circumference of the hips at the level of the great trochanter in order to see whether this bore any correlation to the degree of maturity. The pooled results in

this instance are given for 267 boys aged 12 to 17 examined in 1947 from the four institutions, and are divided first into maturity groups and secondly into year-age groups.

It will be seen that the mean measurements are related more closely to the state of maturity than to chronological age. Thus the means for the pubescent boys at each age are greater than those of the non-pubescent, and those of the adolescents again greater than those of the pubescent boys, irrespective of age. Amongst the boys graded as pubescent (the most homogeneous of the maturity groups), the means are closely similar, whether the boys are aged 12, 13, 14, 15, or 16 years. The differences between the means of the 12 and 15 year-old pubescent boys are not statistically significant.

Whilst there can be only limited value in a measurement which involves at least three variables (bone, muscular tissue, and fat), it is suggested that the circumference of the hips might usefully be included in the routine measurements of prepuberal and adolescent boys.

Physical Performance. Using the same groups as shown in Table 2, a preliminary investigation of physical performance in

TABLE 2. Hip-circumference (cm.) related to Maturity and Age.

Maturity	Mean Age		No.	Mean Circumference	Standard Deviation	Standard Error
	Years	Days				
1. Non-pubescent.....	12	172	35	70.34	3.20	0.54
	13	141	36	72.17	3.51	0.59
	14	216	9	73.22	2.35	0.78
2. Pubescent.....	12	232	19	75.37	2.41	0.55
	13	170	22	76.11	3.88	0.83
	14	163	32	76.82	3.92	0.70
	15	153	15	76.13	4.01	1.04
	16	151	8	75.08	3.22	1.36
3. Adolescent.....	13	234	4	81.38	4.26	2.13
	14	208	30	84.18	4.07	0.74
	15	172	32	85.36	3.98	0.71
	16	168	25	84.29	3.71	0.76

relation to maturity and age was made on the basis of dynamometer readings obtained with grip and pull. The same instrument was used in each case, and the tests carried out as far as possible under standard conditions. The test of pull, however, was the less satisfactory of the two, as the range of readings was relatively small and the pull, being performed with flexed thumbs across the chest at nipple level, cause some discomfort when maximum force was exerted.

The results of the dynamometer tests, arranged as in Table 2, were as follows:

TABLE 3. Dynamometer readings (grip and pull) related to Maturity and Age.

Maturity	Age-group (years)	No.	Grip			Pull		
			Mean	Standard Deviation	Standard Error	Mean	Standard Deviation	Standard Error
Non-pubescent..	12—13	35	69.29	11.93	2.02	22.20	5.64	0.95
	13—14	36	75.17	10.87	1.81	23.72	5.04	0.84
	14—15	9	71.33	11.66	3.89	23.33	3.40	1.17
Pubescent.....	12—13	19	85.63	12.53	2.87	25.00	3.88	0.89
	13—14	22	74.18	9.57	2.04	24.86	4.76	1.01
	14—15	32	83.47	12.22	2.16	25.91	4.89	0.86
	15—16	15	84.87	11.28	2.91	29.27	6.48	1.67
	16—17	8	79.50	4.21	1.49	24.75	4.63	1.63
Adolescent.....	13—14	4	87.50	16.01	8.00	30.50	5.32	2.66
	14—15	30	109.47	17.23	3.15	31.07	5.60	1.02
	15—16	32	116.59	19.72	3.49	31.94	5.04	0.89
	16—17	25	125.79	21.10	4.31	34.88	4.67	0.95

With the single exception of the thirteen-year-old pubescent boys, whose mean grip is less than that of the non-pubescent group of the same age, it is seen that these performance tests increase with maturity rather than age. Thus, with the one exception noted, all the pubescent groups give on the average higher readings than all the non-pubescent, and the adolescent groups higher than all the pubescent groups. The performance of the adolescents

increases with increasing age. This last finding is quite consistent, since as already indicated, the grading of «adolescent» will include both boys who have just passed from pubescence and also those in whom maturity is far advanced. It would be expected, therefore, that the older adolescents would on the average be more mature than the younger ones.

Since dynamometer tests of grip and pull are of limited value in estimating physical performance in general, the above figures are presented solely as a pilot enquiry indicating that physical performance within a limited field is related more closely to maturity than to chronological age. This is consistent with the previous finding, that the mean height and mean weight of boys in each year of age between 12 and 16 is greater in the more mature than in the less mature.

When these observations are applied to boys leaving school at the age of 14 and seeking employment, it is reasonable to assume that their physical status and capacity will be so variable that any attempt to legislate for their protection in industry purely on the basis of chronological age will become largely futile unless formulated in the most general terms. Since the number of adolescents and non-pubescent boys at this age is almost equal, any close definitions of hours of employment, weights which may be carried, etc. are likely to apply most inequitably to the two groups. With the raising of compulsory school-attendance to the age of 15, however, which is to come into force in Great Britain in 1948, the boys reaching the labour market will be in a more uniform stage of maturity, and the number of completely immature boys (who are those most likely to require protection) will become very substantially reduced.

It follows that this mixed group of 14—15 year-old boys will be thrown back on the education authorities, and it is highly desirable that some consideration should be given to their stage of maturity in their grouping and management. This is of course already done in some of the larger and more progressive schools, where doubling of classes makes it possible to educate together boys of approximately the same stage of maturity. Without wishing to over-emphasise the importance of physical status in education, it will

be generally agreed that the physical changes of puberty are associated with emotional readjustments which are likely to react not only on behaviour but also to some extent on intellectual performance. It is suggested, therefore, that the routine use in school medical examinations of some such rough index of maturity-grading as has been described, might have a practical value in the education of boys from 13 to 15. If applied on a large scale, it would certainly throw light on such points as the relationship of age-onset of puberty and male adult height, and the effects of nutritional and genetic factors on the occurrence of late or early maturity.

Summary and Conclusions.

A clinical method of maturity-grading of boys is described which is applicable to routine medical examinations. In the absence of a clearly-defined point corresponding to onset of menstruation in girls, relatively few large-scale studies of the growth and physical performance in relation to maturity in boys have been undertaken. Although of limited accuracy, clinical maturity-grading would make it possible to compare the age-onset and duration of puberty in different social groups and assess the effects of such factors as nutritional deprivation.

The effects of raising the age of compulsory education from 14 to 15 is likely to have a very marked effect on the ratio of non-pubescent to adolescent boys entering the labour market. This should be recognized in formulating legislation for the protection of boys in employment, since the evidence suggests that the height, weight, and physical performance of adolescents is likely to be substantially greater than those of non-pubescent boys.

The information afforded by maturity-grading might well be utilized for grouping boys aged 13 to 15 for educational purposes.

I am indebted to Mr. Luis Sanz for the statistical analyses.

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The Role of Non-Glandular Hormones in Differentiation and Growth.

By G. Lenart, Budapest, Hungary.

Essentially two components contribute to development: differentiation and growth. Even pediatricians and endocrinologists usually consider *childhood* to be the age and the hormones produced by the ductless *glands* to be the guiding factor of development. We cannot dwell on the arguments which oppose this point of view and which claim to prove that the period of development and the period of childhood are not synonyms and that development is directed in the main by other hormones than those of the ductless glands. Suffice it to state that development is nearly finished by the time of birth. If attention is directed to the relative values instead of the absolute ones, the progress made in growth and differentiation is a milliontimes greater during the 9 months of fetal life than in the following 20 years. At this early period of life the ductless glands themselves are mere subjects and not rulers of development. The task of evolution is accomplished by other factors: by the genes acting through their realizators, the gene-hormones.

What are the facts justifying the view that gene-realizators are of hormone character?

Each cell of the organism is capable of producing every gene-realizator because every cell contains all the genes of the fertilized ovum. The domain of the gene-realizators is limited to the cell itself, which is adequate, since adjacent cells as well as remotest ones contain the same genes producing or capable of producing similar active principles. Whereas the glandular hormones act at great distances from the places of their production, the gene-realizators generally remain within the cell: they are produced in the nucleus and act in the plasma. It is for this reason that it was so difficult to prove their existence. At last, KUEHN and his collaborators succeeded in demonstrating that a gene-realizator produced by a flour moth called *Ephestia kuehniella* is, after having been carried to remote organs by the blood current, able to induce

action outside the cell and thus proved its hormone character. *Ephestia kuehniella* has a variety which, unlike the black-eyed variety, has red eyes. Cross-breeding has demonstrated that the color of the eyes is a hereditary monomeric property based on a single gene. In place of the dominant gene of the black-eyed individuals the red-eyed ones have a recessive gene in the homozygous condition. KUEHN's investigations speak in favor of the assumption that the dominant gene need not be present in the corresponding cells of the eye to produce black pigment in it. If various tissues (testicle, ovary, brain) of a caterpillar with the dominant gene are transplanted into a recessive caterpillar, the later develops black eyes instead of red ones. Moreover abundant pigment formation takes place even if the tissues transplanted are not taken from a black-eyed *Ephestia kuehniella* but from another black-eyed species called *Acidalia virgulata*. No doubt the active substance may be carried into the eye by the circulation, besides, it has become evident that in the case of related species the substance is not characteristic of one species only. All these observations speak in favor of the assumption that the active substance is a kind of hormone, which seems to justify our speaking of gene-hormones instead of chromosomic impulses or gene-realizers. Experiments of EPHRUSSI and others demonstrated that these hormone-like substances are extremely rich in nucleinic acids and that too seems to indicate their close relationship with the chromosomes themselves.

These results were confirmed by results obtained with other animals and they are most likely applicable also to the physiology and pathology of animals of higher order and of man.

A light may be thrown upon the role played by the gene-hormones in the physiology of human development by the examination of developmental pathology, i. e. hereditary developmental anomalies. It has been demonstrated that every gene causing an anomaly originates from a normal gene, called its allele gene, which is responsible for the corresponding normal trait. The so-called lethal genes which produce anomalies in the earliest period (morula formation, germ-layer formation, implantation) or cause severe metabolic disturbances leading to the death of the embryo,

are proof positive that in the same period normal segmentation, gastrulation, implantation, i. e. physiologic cellular division and differentiation are also controlled by genes. It is most likely that this control function is exercised by gene- or cellhormones in man too. — The inherited disturbance of periosteal ossification termed osteogenesis imperfecta, further the congenital impairment of the enchondral ossification known as chondrodystrophy are likewise caused by gene-mutation. One may infer from these facts that also under physiological conditions periosteal and enchondral ossification are regulated by corresponding allele genes. The monomeric heredity of elliptocytosis, of night-blindness, of cystinuria prove that the globular shape of the red corpuscles, the normal structure and function of the rods of the retina and finally the decomposition of cystin to urea are due to the action of gene-hormones. The number of instances could be multiplied considerably.

The statements concerning differentiation made above also hold true of the processes of growth. Numerous varieties of nanosomia are known. In the case of a chondrodystrophic dwarf the gene makes its influence felt as early as the fetal period and the anomalies of growth as well as the disproportion of the bones are quite obvious immediately after delivery. Primordial dwarfism characterized by a well proportioned though undersized body manifests itself at the same early period. In HANHART's cases of inherited dwarfism the child develops normally for one or even three years, then his stunted growth becomes more and more apparent if compared with the normal growth of his mates. Another gene brings about a form termed infantile dwarfism. In such cases development is normal until the fourth to ninth year but then growth is suddenly checked and both physical and mental development stop at an infantile level. — The study of chondrodystrophic, primordial, HANHART's and infantile dwarfism showed that even under normal conditions growth, during the various age-periods, is directed by genes.

As a rule genes act through the gene-hormones, however direct influence as in the case of the color of the eye of *Ephestia* is generally exercised only in the first stage of development. Parallely

with the fetal development with its three consecutive periods which may be designated as the *cell-period*, the *tissue-period* and the *organ-period*, the function of the gene- (cell-)hormones is replaced by that of the tissue-hormones and the latter by the organ-hormones furnished by the endocrine glands.

To begin with the process of *differentiation*, of all the tissue-hormones the organizers (SPEMANN) seem to be the most important. The effect is produced by a living organizer can also be achieved by an extract of the tissue containing the organizer. Thus the phenomenon seems to be due to physico-chemical hormone effects. It is probable that the hormone contained in the primitive organizer-tissue reaches its destination by diffusion. Unlike their ancestors, the cell-hormones, which are related to the chromosomes themselves, the tissue-hormones are chemically closely related to the follicle hormone. Early sexual maturity observed in little children in cases of teratoma (ASKENAZY) or pulmonary adenoma (LINER) prove that embryonic tissue-hormones occurring in tumors play a part in differentiation. The tissue-hormones determining sex-behavior are produced not only in tumors but also during the fetal period. In so-called freemartins of cows intersexuality is very likely due to the embryonic male hormones which penetrate into the female partner through the vascular anastomoses which divide the biovular twins.

Embryonic tissue-hormones promote not only differentiation, but also the other component of development, namely *growth*. This has been convincingly demonstrated by the ingenious tissue-cultures of CARREL and EBELING: continued growth of tissue particles cultured on blood-plasma could be maintained by the addition of embryonic extracts but not by the addition of serum alone. Similar favorable results could be obtained by the addition of lymphocytes to the serum. Consequently »growth-lymphocytosis» observed in certain phases of childhood may be considered as one of the causes rather than a sequel of growth as BESSAU believed. Obviously the role the thymus plays in growth is connected with the high number of its lymphocyte elements and this assumption is supported by the fact that growth is generally over by the time the cortex of the organ loses its preponderance in con-

sequence of the rapid decrease of the thymocytes. Under pathological condition the enormous growth promoting energy of the embryonic tissue-hormones is demonstrated by the rapid growth of neoplasms.

Even in the advanced stage of development direction is not assumed by the autochthonic fetal gland-hormones. In the organ-period of the fetus development is influenced by gland-hormones, these are, however, maternal gland hormones which should be regarded *ektohormones*, same as the tissue-hormones of the marine wormlike *Bonellia*, the influence of which causes the parasitical larvae settling down on the proboscis of a female to develop into male individuals while those living free in the water become females. In the human embryo the most important *ektohormone* is the one delivered by the thyroid gland. This is proved indirectly by the fact that in athyreotic newborn infants the symptoms of myxoedema do not manifest themselves unless the mother also is a hypothyrotic. If the hormone production is normal, this maternal *ektohormone* may delay the manifestation of the myxoedema of the infant for some months. For the deficiency or failure of gene-hormone or tissue-hormone production there are no such obvious proofs, a circumstance which, in view of the great importance of these primitive hormones may appear rather paradoxical. It is, however, precisely the great importance that furnishes the explanation because any change that may occur in the production or composition of these hormones may constitute a lethal factor leading to the death of the embryo at a time when it is not yet accessible to examination.

The significance of the cell- and tissue-hormones gradually recedes into the background in the course of infantile life partly because the speed and domain of differentiation and growth decrease rapidly, partly because the adequate stimulus in the post-natal «organ-period» the appropriate stimulus is provided by the «organ-», i. e. gland hormones. Nevertheless the tissue-hormones continue to play their part in differentiation even after the bulk of the organisation has been concluded. In proof of this I should like to refer only to Castle's intrinsic factor of the gastric mucosa, the absence of which involves a disturbance of the normal

development of the erythrocytes, namely the formation of megalo-blasts instead of normoblasts.

In an examination of the correlation of cell-hormones, tissue-hormones and organ-hormones the question arises: what, in the course of development, may be the cause of the transference of hegemony from the gene-hormones to the tissue-hormones, from the latter to the placental hormones, later on to the ekto-hormones and finally to the autochthonic glandular hormones? The problem bears a close relation to the gene-manifestation. There is no space here to deal with this problem in detail though it constitutes a fascinating chapter of the genetic physiology of development. It may suffice to mention that each gene-manifestation is associated with an adequate «critical» or «sensitive» period during which in its more or less important sphere of action the gene-hormone contributes to the organisation.

The term «sensitive period» has first been used when experiments performed with butterflies showed that the phaenical manifestation of the single gene is strictly limited to a certain period of development. The plasma substance of the cells or cell groups being different (only the both quantitatively and qualitatively even distribution of the genes but not that of the plasma is accomplished by cell-mitosis) the cells will respond differently to the identical hormones of their identical genes, i. e. they will not react to certain hormones unless at that particular time their plasma is in a sensitive period in relation to these particular hormones.

Like most elements in the body of physiologic knowledge this too has been derived from the pathologic processes (action of thermic conditions on butterfly larvae and so on). Observations recently made in Australia and in the United States seem to indicate that in man too it is such sensitive periods that determine the activity of the gene-hormones. It is common knowledge that the rubella of pregnant women leads to cataract, heart lesion or other congenital malformations in the infant provided that the rubella manifests itself during the first three months of pregnancy. In a later phase rubella will not result in similar alterations, obviously because the sensitive period of the crystalline lens, etc.,

in respect to the responsible hormone does not coincide with that particular period of intrauterine life.

We must be prepared to meet with sensitive periods also in the case of endocrine disorders in the postnatal period. Following the long siege of Budapest the number of goitre cases has considerably increased among children from 4 to 7 years of age. This phenomenon, being limited to the age group mentioned and independent of sex, was probably due to starvation, cold nervous strain and other circumstances of living in cellars for more than two months. This elective affinity unobserved after the first war may have been due to a kind of sensitive period. In similar cases the investigation of the peristatic disorder and that of the sensitive period may be of great help in trying to prevent the damage. It would be wise to pay attention not only to the locus but also to the *tempus minoris resistentiae*.

Endemic Goitre in Children.

By Professor **O. D. Sokolova-Ponamarova**, Omsk, USSR.

Correspondent-member The Academy of Medical Science of the USSR.

The problem of endemic goitre is very complex, representing great scientific and practical interest. Endemic goitre is widely spread throughout the world. The populations of Switzerland, Italy, Germany, France, the territories of the Carpathian Mountains, the Pyrenees are most of all exposed to the disease. There are areas of endemic goitre in Africa, Asia, Eastern Tibet, on the slopes of the Himalaya. In the U. S. A. goitre is observed in the Cordilleras, and other mountainous regions, also in the states east of the Cordilleras and in the region of the Great Lakes: Wisconsin, Michigan, Dakota, Minnesota.

In the Soviet Union foci of endemic goitre are found in the Urals, in certain parts of the Caucasus, in districts of the basin of the Upper Volga, in the Mariisk Autonomous Soviet Socialist Republic. In Siberia, endemic goitre has been reported from the Irkutsk region, near Lake Baikal, along the valley of the Lena river and in Oirotia Altai region.

The spread of endemic goitre is connected with certain geographic regions. Endemic goitre in its development shows special regular features, a common formal and causal genesis. The intensity and the development of endemic goitre vary and depend on the strength and nature of the factor determining its appearance as well as on endogenous and exogenous causes and their inter-relationship.

On the basis of research carried out in the USSR and complex study of the foci of endemic goitre by Soviet scientists, Nikolajev, O. V., Levitt, V. S., Miloslavskij, V. V., Sacharov, V. V., Ljapunstin, V. A., Achrem-Achremovitch, R. M., Slonim, M. I., Shipatch, V. G., Aslanishvili, I. A., Masumov, Syzganov and others, certain new scientific data were found and used as a basis for prophylaxis and therapy. They have provided practical proof of the data found.

During the study, a causal relationship was found between the appearance of goitre in certain localities and the lack of iodine, thus confirming the basic elements of Shaten's theory regarding the role of iodine in the etiology of goitre.

By means of pathohistological research it was found that there is no principal or considerable difference between the two nosological forms of goitre — the mountain and valley goitre.

Scientific expeditions carried out in the Soviet Union confirmed the assumption that goitre in endemic localities is not the only sign, but only one of the more apparent signs of the influence of the «strumogenic» factor on the entire organism. Our own observations of endemic goitre in children in Oirotia, studies of the cardio-vascular system, the hemopoietic apparatus a. o. in children with goitre as well as in children without goitre and the corresponding findings in adults by Prof. Achrem-Achremovitch have confirmed this fact.

Studies and prevention of endemic goitre in the USSR is a most important government public health problem. Several anti-goitre stations were opened in the Caucasus, Urals, in the Mariisk Autonomous Republic. A wide net of anti-goitre stations were organized where goitre was prevalent. The problem is being studied in the Moscow and Kharkov Endocrinological Institutes. Several scientific expeditions for the study and prevention of

endemic goitre were sent by the Government to all endemic areas. All this work is unified by the Central Goitre Commission of the Scientific Medical Council of the Ministry of Health of the USSR.

The achievements of the Soviet scientists were used as a basis for the widely spread preventive measures against endemic goitre performed in the USSR on a governmental basis, and take into account the experience of foreign countries, with the result that endemic goitre has considerably decreased. Under present conditions, in view of the relatively limited occurrence of goitre in some regions of our country, it would be more correct to speak of an endemic enlargement of the thyroid, rather than of goitre. For instance, in Kabarda where over 50 per cent of the population had goitre, endemic goitre was practically eliminated and in 1941 only 0.9 per cent of the population had goitre. The prophylactic measures in the fight against endemic goitre, were, first of all, applied to the child population.

Endemic goitre in children has been somewhat neglected in the literature. In connection with studies of endemic goitre in adults, there are short references to the occurrence of goitre in children. But the clinical study of endemic goitre in children is of great importance in the fight against goitre. It is known that in endemic areas a large percentage of goitre occurs in childhood, mainly in the period of sexual maturation. Endemic goitre is seen in children at a very early age and can at times be congenital.

The physiological role of the thyroid gland is very important, especially for the growing organism. The thyroid gland is a rather labile organ and this lability is more marked in children, mainly in girls. Suffice to point out the «physiological swellings» of the thyroid gland in the newborn and during puberty, also during menstruation. The diffuse enlargement of the thyroid gland in the period of sexual maturation is of a transitory nature and may not lead to the development of goitre. In the presence of endemic goitre, the first phase of enlargement of the thyroid gland, which is closely associated with the development of pathological processes, must be regarded as «a hyperplasia, physiological or borderline pathological» (Nicolajev, O. V.).



Fig. 1. Two children of one family diffused thyroid glands goitre of 3rd degree.

The weight of the thyroid gland was shown to be higher in endemic areas than in areas free of goitre.

Thus the normal size of the thyroid gland can be spoken of only under due consideration of age, of sex and of geographic conditions of the area. All this makes it difficult to attain an exact determination of goitre.

Since we participated over a period of several years in the work of scientific expeditions for the study and prevention of endemic goitre, we had the possibility in Oirotia to study the peculiarities of the clinics of endemic goitre in children.

The method of examination of the thyroid gland in children, mainly in the newborn, presents occasionally considerable diagnostic difficulties. In examining the thyroid glands in children I used my own method to determine quickly and easily the form and size of the thyroid gland in the child. Examination of the thyroid gland was performed by inspection with the head of the child

slightly tilted back. In this position the thyroid gland is outlined more distinctly and its measurements can be taken with greater accuracy. Its consistency is determined by palpation.

Analysis of the material of scientific expeditions have established the fact that goitre in Oirotia is endemic, is encountered in an average of 17.4 per cent and belongs to goitre of medium weight.

Studies of endemic goitre in children of Oirotia have shown that the percentage of goitre in infants under three years is slight and equals an average of 1.6 per cent. In the age group of 3—6 years there are 10.2 %, in the age group of 7—12 years 19 % with a maximum for the age group of 13—19 years up to 21.7 per cent.

Girls affected with goitre are in the majority, beginning with the age of 7—12 years. In the next age group 13—19 years, the sex difference is expressed still more strongly.

Grouping the examined children and adolescents by degrees of thyroid gland in accordance with the Swiss classification, shows that most often the second degree of thyroid enlargement was encountered particularly in the age group 7—12 years. Other degrees were noted correspondingly less frequently, and the fourth degree among infants under one year of age was not noted in a single case. Our extensive anthropometric data, which we cannot present here, showed that the physical development of children in Oirotia, both goitrous and nongoitrous, is quite satisfactory.

We found in children the diffuse form of goitre to be prevalent, which confirms the findings published in the literature. Goitrous children in Oirotia had the following shapes of goitre: 1) horseshoe, 2) horseshoe with a stronger involvement of the right part of the gland, 3) knotted, 4) mixed, and 5) the so-called «fat neck». By far most of the goitrous children were noted to have the horseshoe shaped type of the horseshoe shaped one with a stronger growth of the right part of the thyroid.

The clinical picture of endemic goitre of children in Oirotia, particularly the function of the thyroid gland and the cardiovascular system of the goitrous children, gives reasons to place in most cases goitre in Oirotia under euthyreosis with certain, not very marked features of hypothyreosis. Clinically goitre in the children in Oirotia was characterized by a lack of any complaints



Fig. 2. Boy 13 years old, goitre 3rd degree much enlarged on right side (diffused goitre).

on the part of the goiterous as well as of the nongoiterous children. There was not a single case in which we could find signs of the so-called «mechanical» and thyrotoxic goitrous heart among either the goitrous or the nongoitrous children. Clear clinical changes of the heart were not encountered among either the goitrous or the nongoitrous children.

Blood pressure of the goitrous and nongoitrous children showed a tendency to decrease in comparison with the blood pressure of healthy children living outside the endemic locality. The blood pressure of the goitrous children showed lower figures.

Studies of the cardiovascular system likewise showed slight functional insufficiency, which were apparent more distinctly among the goitrous children.

Studying the conditions of the capillaries of the nail bed of goitrous children in Oirotia, it was found that normal capillaries occurred in 33 %, capillaries — type vasoneurotic diathesis in

59 %, dwarfed capillaries in 17 % of the cases. In non goitrous children normal capillaries were found in 60 %, vasoneurotic diathetic type in 30 %, and in 10 % of the non goitrous children dwarfed capillaries were found. The frequency of capillaries of the vasoneurotic diathetic type increased with the higher category of the thyroid gland. The capillary changes are an additional feature characterizing the endemic goitre in Oirotia as an euthyrosis with some inclination to hypothyreosis.

The severity of a goitre endemic is characterized by the presence of congenital goitre.

The presence of struma congenita in endemic localities evidences the intensity of the strumogenic factor and stresses the necessity to undertake prophylactic measures. Published data in the literature establish the fact, that in areas of endemic goitre, the thyroid gland is enlarged in the majority of the newborn. This enlargement of the thyroid gland is regarded as a beginning hyperplasia, which will lead to goitre formation eventually. The weight of the thyroid gland in cases of Struma congenita can be very high and may cause a peculiar clinical picture, with very severe disturbances and may occasionally threaten the life of the child.

Cases of congenital goitre, as described by Demme, Eggenberger, Feer and others illustrate this condition.



Fig. 3. One month old baby congenital goitre.

In the investigations of the scientific expeditions regarding the studies of endemic goitre in the USSR, the rarity of congenital goitre is mentioned. Gigantic increases of the thyroid gland and heavy disorders are not described in any of the cases.

The question of etiology and pathogenesis of congenital goitre has not been solved at the present time.

Some investigators considered heredity an important factor in goitre, especially in congenital goitre.

The work of Soviet scientists (Nikolajev, Slonym, Sakharov and others) has determined that goitre is not hereditary and parents who have had goitre may have children who will be absolutely healthy. A child in the womb of its mother can be affected with goitre just the same as its mother, by those pernicious influences of the surroundings which are the causes of goitre.

During my investigations I saw a child only one month old whose thyroid gland at the moment of birth was as large as an egg, but showed no pathological signs of strumogenic perniciousness. On repeating the examination four years later, the thyroid gland of this child was found to belong to the second degree. The general development of the child was good.

Among the areas of endemic goitre in the USSR cases of cretinism were found in the past in Pamir, in the Urals, in Marijskaja ASSR, in Eastern Sibirija and in Eastern Bukovina. Among the children living in Oirotia whom I examined, there was not a single case of cretinism or of conditions similar to cretinism; likewise, there was no hyperthyreosis.

Along with a normal content of hemoglobin and erythrocytes among the goitrous and the nongoitrous children of Oirotia, cases of mild anemia were noted: this was more distinct in the cases of the goitrous children. The content of reticulocytes was usually within the norm or slightly less, and was present equally in goitrous and nongoitrous children. Most of the children who were studied had thrombopenia, which was more distinctly evident among the nongoitrous children. The sedimentation rate both of goitrous and nongoitrous children in most cases was normal or showed inconsiderable acceleration.

Fifty per cent of the studied children had leukopenia, which

was more evident among the goitrous children than among the nongoitrous ones. The Schilling leukocytic blood formula for the studied children in Oirotia both for goitrous and nongoitrous is characterized mainly by lymphocytosis, slight shift to the left, eosinophilia and monopenia.

In characterizing the clinical picture of endemic goitre and the functional conditions of the thyroid gland of the children in Oirotia, in most cases it should be termed *euthyreosis*. At the same time it should be stressed that in certain cases special features inherent to indistinct forms of hypothyreosis were noted.

The mass iodine prophylaxis which is being performed in accordance with the instructions of the Ministry of Health of the USSR, as a public health measure, has shown good results as evidenced by the abrupt steep decrease of goitre in Cabarda on the Caucasus from 58 % down to 0.9 %, and where the heavy forms of the 3rd and 4th category changed to lighter forms and became rarities.

Treatment of endemic goitre in children consists of giving small doses of iodine. In most cases, systematic iodine prophylaxis is at the same time the method of treatment. Surgical treatment of goitre among children is used very rarely and for diffuse forms of goitre of *euthyreotic* nature surgery is contraindicated. At the present time scientists in the USSR continue their investigations into the etiology, pathogenesis, clinics and a more rational prophylaxis of endemic goitre.

The success in prevention of endemic goitre in the USSR is due to the great care which the Soviet Government extends to the people and particularly to the child population.

Section 8—Miscellaneous Topics.

Eight Hundred Cases of Poliomyelitis Treated in the Sahlin Respirator.

By **Rolf Bergman**, Stockholm, Sweden.

A preliminary report on 827 cases of poliomyelitis suffering from respiratory troubles treated in the Swedish made Sahlin-Stille respirator. 542 succumbed while still in the respirators. In these cases the fatalities were due to circulatory paralysis. In addition 37 cases died some time after they were released from the machine; the reason seems to be that they still had a relative paralysis of the respiratory muscles. The number of surviving cases thus is 126 or 15 per cent, which by far exceeds the general Swedish mortality rate in poliomyelitis (10—20 per cent; 1947 only 6 per cent). Those — indeed many — cases, whom we cannot save by the respirators, are although spared for the torments of suffocation.

90 of these 126 surviving cases were followed up and recently investigated in order to get an opinion of the social and occupational capacity. 30 cases i. e. 33 per cent of the investigated were invalides, 41 (46 per cent) were partially disabled; the number of treated persons, who could be considered to work and to earn their own living was 19 i. e. 21 per cent. These means that 2 per cent of all treated cases could be saved to a useful social life.

Report on Treatment of Asthma Bronchiale in Children in Finland.

By **Zaida Eriksson-Lihr**, M. D.

Chief Physician of the Hospital Allergic Disease, Drumsö, Finland.

Bronchial Asthma is rather frequent among children in Finland and the number of cases seems to have increased during the war.

243 children, suffering from bronchial asthma were treated polyclinically during the last 10 years. (The first hospital for allergic disease was erected this year.)

139 (57.2 per cent) were boys and 104 (42.8 per cent) were girls.

209 (86.2 per cent) of the cases had a family history of allergy, 88.5 per cent of the boys and 82.7 per cent of the girls.

The *profession of the father* was in 51.8 per cent that of manual worker or of lower official, in 48.2 per cent that of the free professions or of higher official.

137 cases (56.4 per cent) had been or were still suffering from allergic skin manifestations. (59.7 per cent of the boys and 51.9 per cent of the girls.)

19.4 per cent of the boys and 31.7 per cent of the girls still had eczema or Prurigo Besnier, when they came for special treatment for asthma.

The age of onset of asthma bronchiale was:

below 1 year	39 cases (16.1 per cent)	boys 18.7, girls 12.5 %
» 5 »	185 » (76.1 » »)	» 75.6, » 76.9 %
» 10 »	230 » (94.6 » »)	» 95.0, » 94.1 %

The duration of the bronchial asthma before special treatment was started was

Years	Number of boys	Number of girls	Total
1	43	24	67
1	23	18	41
2	21	14	45
3	11	13	24
4	10	10	20
5	6	10	16
6	8	3	11
7	5	2	7
8	3	5	8
9	1	0	1
10	3	3	6
11	4	1	5
12	0	0	0
13	1	1	2
	139	104	243

Number of Eosinophiles in the blood:

below	5 per cent	in	32.8 per cent	of the cases
»	10 »	»	» 35.9 »	» » » » »
over	10 »	»	» 31.3 »	» » » » »

The *treatment* was partly unspecific, partly specific desensibilisation. In order to establish the result of the treatment an inquiry was sent to the parents of the 243 children. 198 answers arrived.

Of those 198 children 176 had received a full treatment,
22 had interrupted their treatment.

Of the 176 fully treated cases

146 (83 per cent) had been free from attacks at least one year.

27 (15.3 per cent) were much better

3 (1.8 per cent) showed no improvement.

Of the 22 cases, which had interrupted their treatment too early:

3 (13.6 per cent) had no more attacks,

3 (13.6 » ») were much better,

7 (31.8 » ») showed some improvement,

8 (36.5 » ») showed no improvement,

1 (4.5 » ») had died two years after the last treatment in a severe attack of asthma, first being one year free from attacks after treatment had been interrupted.

The Importance of Kathepsin for the Protein Digestion in the Stomach.

By **E. Freudenberg**, Basel, Switzerland.

Until a short time ago the mechanism of protein digestion in the stomach was not properly understood because during the greater part of the time during which the food remains in the stomach, the p_H is rarely found to be below 3.0. During the third hour after food ingestion the p_H of the chyme may be equal or

below 3.0, but by this time most of the chyme has already left the stomach. From our present knowledge we may thus say that either the stomach juice is active and the acidity sufficient, but with little or no chyme to work on, or there is plenty of chyme, but the acidity is insufficient and the enzyme not active enough. As things are it has even been discussed that the infantile stomach is only a reservoir like the ingluvies of the ruminants. That this conception is wrong can be proved by introducing a duodenal tube and feeding the child in the normal way. When samples of the chyme are then withdrawn by the tube they show that a maximum of up to 2/3 of the protein is digested.

Since 1940 we have known that apart from pepsin with its rennet factor another proteolytic enzyme, kathepsin, is contained in the stomach juice. This enzyme is a pure protease like pepsin. In 1940 we had assumed that the optimum of its action was at p_H of 4.7. Working upon this assumption we found that without activation its effect was 60—80 % of the pepsin effect under otherwise equal conditions. We know to-day that the optimum of kathepsin lies in a more acid medium, viz. at p_H 3.4. *Ceteris paribus* we find now that without activation the effect of kathepsin compared with that of pepsin is 1:1. The proof of the presence of kathepsin has been made easier by a method which Dr. Buchs evolved in our laboratory in order to measure the »Substratschwund», i. e. the decrease of the protein during proteolysis. I am showing you examples of gastric juices, estimated by this method, which prove that the gastric juice contains two proteolytic enzymes and not only one. Apart from human juices we have used juices from the rennet bag of the calf and of pig stomach; a commercial pepsin preparation is also demonstrated.

Pepsin and kathepsin differ in the following ways:

- 1) they have different optima of reaction,
- 2) they have different optima of temperature,
- 3) only kathepsin is activated by H_2S , Cysteine and HCN , not pepsin,
- 4) the resistance against ultraviolet light is different; kathepsin is more resistant,
- 5) kathepsin has no rennet factor.

On the other hand the two enzymes have the following qualities in common:

- 1) the optimum of their stability is found at the same degree of acidity (p_H 3.8),
- 2) they act on the same nutrients,
- 3) they are both pure proteinases,
- 4) the kinetics of reaction are the same for both; they follow the rule of Schuetz,
- 5) the two enzymes occur in a constant proportion in the gastric juice and in the gastric mucous membrane,
- 6) during growth the two enzymes increase equally as the years pass,
- 7) separation fails, it is only possible to stop one constituent completely.

We are under the impression that there is only one gastric protease in existence, but that it produces different effects: the pepsin effect, the rennet effect, the kathepsin effect, missed up to 1940, and the plasteine effect. How this single protease is able to exert its different functions remains to be investigated. For the time being there are only conjectures of which the most useful one appears to be the following: that the enzyme proteine is altered under the influence of exogenous circumstances (p_H , temperature) in such a way that a complex with new qualities is created.

Gold Compounds in the Treatment of Chronic Arthritis in Children.

By **T. Halbertsma**, Haarlem, Netherlands.

Mr. President, Ladies and Gentlemen:

In presenting to you my paper about gold-therapy in chronic arthritis of children, I want to speak to you about a disease against which, until recently, there existed no cure.

This is curious because in treating adult cases in Europe, gold has for several years proved its curative effect. It was Forestier in France who in 1929 was the pioneer of gold-therapy, which

spread quickly all over the continent of Europe. According to Snyder and Traeger, England followed about 1937, and it was Hench who in 1939 published results of the first American cases.

Gold is a potent but dangerous drug. In the beginning too large doses were given and there were accidents, toxic reactions; there was purpura and agranulocytosis, and sometime fatalities. An indication of imminent danger is a rise of the eosinophiles.

In my country the general opinion is that gold is an important acquisition in therapy, especially in fresh cases of chronic arthritis. In older, atrophic cases it is useless. In adults, the best method is one where small doses are used. The blood should be checked regularly. After some weeks the sedimentation rate usually declines, the temperature also drops, the swelling and pain in the joints also decreases and in many cases the patient is cured in some months. We in Holland have now treated several children with gold and our opinion is that it is the only therapy which is effective.

My experience of this treatment is very favourable because all the cases of chronic therapy which I saw were apparently cured. It is possible that my cases were of a special type and, therefore, I will show you presently some lantern slides with details of these cases.

But first, something about the method of administering the gold. I used Solganal B., a 2 % suspension of auro-thio-glucose: this compound contains 50 % pure gold, so that every injection of 0.1 cc contains 1 mgr pure gold. I injected twice weekly 0.1—0.4 cc. Solganal, that means 1—4 mgr gold twice weekly. A series of 10 injections was followed by an interval of several weeks, after which further series of injections could be given if considered necessary.

The blood was examined regularly but, with our small doses of gold, we never had any serious deviations: there was never leucopenia, although we often noticed a rise of the eosinophiles. Figures of up to 20 % eosinophiles were frequent but it soon became apparent that it was not necessary to interrupt the injections when using small doses of 1—4 mgr gold.

I gained the impression that the injections had an immediate effect on the sedimentation rate, which reached normal, or nearly

CASE I. Willy Nederkoorn, old 14 years. Girl. High fever, exanthemata. Swollen hands and feet. Involvement of fingers and toes, and all possible joints. Subcutaneous nodules.



Date	Sedimentation rate
2 June '37	56/86
13 June '37	88/99
4 Nov. '37	68/110
5 Apr. '38	92/120
Sept. and Oct.	Ten gold injections
12 Jan. '39	56/84
Jan. and Feb.	Ten gold injections
25 Feb. '39	54/90
May and June	Ten gold injections
11 July '39	77
3 Oct. '39	47
Oct. and Nov.	Ten gold injections
28 Nov. '39	35/69
17 Feb. '40	35
24 May '40	30/59
11 Sept. '40	7/14

Result: very good after one year treatment.

CASE II. Henk Bruines, old 8 years. Boy. Middle grade fever. Exanthema. Slightly swollen fingers; involvement of a vertebra, a hip joint and an ankle. Hypochromic anaemia.



Date	Sedimentation rate
22 Sept. '40	101 mM
7 Oct. '40	78/112
11 Oct. '40	75/84
Oct. and Nov.	Ten gold injections
25 Oct. '40	62/90
8 Nov. '40	45/78
14 Nov. '40	19/39
16 Mrh. '41	3 mM

Result: total recovery.

normal rates at the end of the treatment. Some children needed 3—4 courses of injections, other children only 1—2. In effect, during the whole treatment we were guided by the sedimentation rate. Furthermore, in case of complicating anaemia, we treated the child also with a combined iron and liver therapy. No gold therapy was started until salicylates and sulfadruugs proved themselves useless.

CASE III. Elsje van Oplo, old 6 years. Girl. High fever. No exanthema. Involvement of elbows, wrists, ankles a. s. o. Leucocytosis. Hypochromic anaemia. Eosinophiles up to 20 % during gold therapy.



Date	Sedimentation rate
15 June '42	108/128
13 July '42	86/114
July—Aug.	First ten gold injections
18 Apr. '42	56/93
Sept.—Oct.	Second ten gold injections
20 Nov. '42	23/48
28 Dec. '42	4/13

Result: remained well until the beginning of 1947.
Recidive (?).

CASE IV. Truusje van der Heyden, old 5 years. Girl. Exanthema, high fever. Involvement of different joints, a wrist, a shoulder, some fingers. Slight anaemia.



Date	Sedimentation rate
10 Oct. '38	117/130
14 Nov. '38	82/102
29 Dec. '38	36/71
25 Jan. '39	25/53
13 Feb. '39	82/94
March—Apr.	First ten gold injections
22 Apr. '39	78/104
13 May '39	56/83
June—July	Second ten gold injections
21 July '39	32/54
12 Aug. '39	13/28
2 Oct. '39	8/18

Result: total recovery.

I now want to show you some lantern slides with details and figures concerning the seven patients I treated with gold. On these slides the inflicted joints are marked. In my tables I have given figures only for the sedimentation rates and the gold injections, as it was impossible to give concise details of other symptoms, such as fever, degree of swelling and pain in the joints.

The *first* case was that of a girl with an inveterated chronic arthritis, with severe general symptoms such as high fever, skin eruptions, rheumatic nodules, etc. From the table it is evident

CASE V. Peter Christiansen, old 5 years. Boy. Both wrists and ankles and nearly all his fingers and toes painful and swollen. No anaemia.

During gold treatment eosinophiles up to 18 %.



Date	Sedimentation rate
3 Sept. '42	21/46
Sept.—Oct.	Ten gold injections
3 Oct. '42	21/48
4 Dec. '42	16/38
25 Jan. '43	23/51
Feb.—March	Ten gold injections
8 Mrh. '43	18/34
19 May '43	12/21
21 June '43	8/18
23 Aug. '43	7/12
18 Dec. '43	6/14

Result: very good.

CASE VI. Wendela Beuker Andreae, old 4 years. Girl. Slight feverish case. Both knees, one elbow and one ankle involved. During therapy 10 % eosinophiles.



Date	Sedimentation rate
25 Oct. '43	12/13
Nov.—Dec.	Ten gold injections
8 Dec. '43	35/70
6 Jan. '44	25/56
Jan.—Feb.	Ten gold injections
26 Jan. '44	25/59
25 Feb. '44	34/67
25 Mrh. '44	20/57
19 Apr. '44	20/60
Apr.—May	Ten gold injections
6 June '44	11/33
7 July '44	25/61
July—Aug.	Ten gold injections
20 Aug. '44	24/58
30 Nov. '44	18/39
21 Dec. '44	6/14

Result: good, but for a slight limitation in the extension of both knees.

that the sedimentation rate decreased after each course of injections, and ultimately the child was cured after one year treatment.

The *second* case had similar but less severe symptoms. Here recovery occurred after only one series of injections.

The *third* case was still less serious. This child showed a marked

CASE VII. Marijke de Vries, old 5 years. Girl. Painful and swollen wrists and ankles. No fever. Anaemia of the hypochromic type.



Date	Sedimentation rate
26 Apr. 1947	21/38
April—end June	Eighteen gold injections
19 May 1947	18/30
12 June 1947	7/18
21 June 1947	7/15

Result of gold therapy: until further notice satisfactory; ankles cured, the wrists still stiff and thickened but painless.

increase of the eosinophiles, which we learned not to fear. Although they reached as high as 20 % we continued our injections, and we even had a good impression of this reaction of the blood.

Case *four* was also a case with strong general symptoms. The child made a total recovery after two series of injections.

The *fifth* case showed no general symptoms. He suffered only from swollen joints and could not use his fingers because of the pain. Eosinophiles up to 18 % under gold treatment. Total recovery.

Case *six* was that of a girl with slight but very obstinate symptoms. We needed 4 courses of gold to get the sedimentation rate down and the child remained slightly crippled, because there is still a slight limitation in the extension of both knees. The general condition is very good now: the sedimentation rate normal.

The last and *seventh* case is a new case which I have still in the hospital. Only wrists and ankles are affected and I treated her with a continuous series of 18 injections. As the eosinophiles rose at last up to 24 %, I stopped injecting gold some weeks ago. The pain and swelling of the joints has disappeared; there exists still a stiffness and swelling in both wrists.

Comment. It is obvious that my cases all had some traits in common. All were relatively light cases, with slight swelling of the joints, several had high or moderate fever, and all were in an active

phase. Except for the first, all were fresh cases. In all cases the sedimentation rate was high. All were cured, and with the cure the sedimentation rate became normal. This uniformity may possibly explain why the treatment of different sorts of cases by other pediatricians showed less successful results.

In *conclusion*, I am of the opinion that gold is a very valuable acquisition in the therapy of chronic arthritis of children, and deserves further publicity. Good results can be obtained, especially in light cases and cases with general symptoms and a high sedimentation rate.

Le Brachy-oesophage chez le nourrisson.

Par le Professeur **Marcel Lelong**, Paris.

La brièveté congénitale de l'oesophage (ou brachy-oesophage) avec présence dans le thorax d'une partie plus ou moins grande de l'estomac est une malformation qui n'est pas très exceptionnelle quand on la recherche systématiquement chez les nouveau-nés et les nourrissons vomisseurs habituels. Les régurgitations glaireuses et les hématomésos intermittentes sont en faveur du diagnostic; elles résultent de l'oesophagite associée. Dans les premières semaines de la vie la maladie peut aboutir à un état de dénutrition grave.

L'image radiologique de cette malformation est typique. Elle se distingue de celle des autres affections de l'oesophage. Elle se sépare nettement de celle de la hernie trans-diaphragmatique de l'estomac.

Le brachy-oesophage est une malformation de l'oesophage; la hernie de l'estomac est une malformation du diaphragme; la soi-disant hernie hiatale n'est pas une hernie, mais une ectopie de l'estomac.

Passés les premiers mois de la vie, le brachy-oesophage a le plus souvent une évolution favorable. Les troubles fonctionnels et la dénutrition qui en résultant cèdent à un traitement médical très simple: la position orthostatique pendant et après la tétée. Il n'y a jamais d'indication chirurgicale.

Some Recent Developments in our Knowledge of Renal Function in Infancy.

By R. A. McCance.

Department of Experimental Medicine, Cambridge, England.

The effect of age upon form has been very well investigated, but the effect of age upon performance i. e. function has been very largely neglected by the physiologists, and nearly all the developments in infant physiology have been made by clinical men. We have been interested for 8 or 9 years in the physiology of the kidney in infancy. The war held up our work for some time but we made a fresh start some years ago, and I would like to outline some of our findings to you today and mention their application to clinical medicine.

It is common knowledge now that the glomerular filtration rates and the urea clearances are very low in infancy. The sodium and chloride clearances are also very low, and this is one of the reasons why newborn and premature infants are so liable to oedema. The comparison with adults is usually made on a basis of surface area. I need not go into any of this work now for most of it has been published for some years. The discoveries were made on both sides of the Atlantic and I have myself reviewed them in a lecture which I had the opportunity of giving last year in Switzerland. (McCance, 1946.) In recent years our work has been developing in several directions. We have been studying the kidney functions of some newborn animals and comparing them with human infants, and we have also been studying the enzymes and membrane properties of infants' kidneys, but time prevents me from going into these matters today. I wish, however, to say a word or two about some investigations of tubular function in infancy which Dr. Dean and I have made. (A Table will be shown giving a summary of this work.) There is nothing new about the inulin and urea clearances. You will notice, however, how low the diodrast clearances are in infancy. They are low, not only absolutely, but also relatively to the inulin clearances, which are now (following the fine work of Dr. Homer Smith in this city) generally

taken as measuring the glomerular filtration rates, and as a general standard of reference for so much renal physiology. This suggests that the tubule cells at birth have not yet developed the adult capacity to excrete diodrast, and it explains why it is so difficult to visualize the pelvis of an infant's kidney by intravenous pyelography. It is also clear that even if diodrast gives a measure of the blood flow through the tubules later in life, it can certainly not be trusted to do so in infancy without much further work. You will notice again that the creatinine clearances are higher than the inulin clearances in adult life. This is generally attributed to the excretion of some creatinine by the tubule cells. In infancy the two clearances are the same, suggesting that this tubular function also is undeveloped at birth. It is interesting to note in passing that in most mammals the tubule cells do not excrete creatinine, so that in this respect the human infant resembles the adult dog, rabbit, rat, and other animals.

We have also made some investigations of the pH, titratable acidity, ammonia and phosphate excretion in infancy. For this, urines were collected at all hours of the day and night from infants aged 0—7 days and from adults. These studies have one rather attractive feature. A comparison of the results for infants with those of adults does not involve any standard of reference such as surface area, which is always rather an uncertain quantity. The average pH value of the urine in the first 7 days of life is the same as it is in later life, i. e. about 6, but the individual figures do not vary so much about this mean as they do in later life, and the averages are rather lower in the second and third days than they are at birth or later.

My next point is that the ammonia coefficients tend to be higher in infancy than in adult life (a histogram will be shown to demonstrate this). Furthermore, more of the acid excreted by the kidney uncombined with fixed base is linked to ammonia. (A histogram of these relationships will be shown.) This suggested to us that the urine in infancy must be short of some of the buffer substances which contribute so much to the titratable acidity of adult urines, and we at once found this to be true. An infant's urine may contain practically no inorganic phosphorus, and a

comparison with adults is best made on the basis of the total N of the urine, for this virtually eliminates the complications of the urine concentration being so different at the two ages. (A histogram will show a comparison.) The inevitable result of this phosphate deficiency is that organic acids account as a rule for nearly all the titratable acidity of an infant's urine, whereas they usually only account for some 20—50 % of the titratable acidity in an adult's urine. (A histogram will be shown to demonstrate this.) It is hardly necessary to add that the phosphate clearances of infants have been found by us to be very much lower than those of adults. (A chart will summarize this work.)

The phosphates excreted by an adult are a valuable vehicle for the excretion of acid uncombined with base. I need not elaborate this matter here, for I am sure you are all familiar with the work of Gamble, and more recently Pitts, in this connection. I must, however, point out that the paucity of phosphates in many infant urines must be a handicap to the infant in excreting acid. It has often been argued whether the newborn infant is or is not in a state of acidosis. Our own results do not enable me to say one way or another, but they do indicate that infants may be badly equipped so far as their kidneys are concerned for dealing with an acidosis, should one arise.

McCANCE, R. A. (1946). *Schweiz. Med. Wochenschr.* 76, 857.

Pancreatic Function in Different Clinical Conditions.

By **Peter V. Véghelyi**, Budapest, Hungary.

This paper is a report of some results of observations of the external secretion of the pancreas. For the examinations, the pancreatic juice was collected by a simple tube but when this reached the duodenojejunal flexure a second tube was introduced into the stomach to aspirate both the secretion and the saliva swallowed. No special stimulant or secretin was used.

I have used various methods of enzyme determination in the course of several years, such as the stalagmometric method of Rona and Michaelis (1), that of Willstätter (2) and the photometric

one of Leubner (3) for lipase; the method of Michaelis (4) or that of Ågren and Lagerloef (5) for trypsin; and those of Wohlgemuth (6) and Ågren and Lagerloef for amylase. As every method yields different figures for normal values, for purposes of comparison the lowest limit of normal will be expressed as 100 per cent. This corresponds, for instance, to 160 Wohlgemuth amylase units, or to 0.60 units (that is 1.20 ml of NaOH) in Ågren's and to 128 in Michaelis' trypsin estimation, or to 5 per cent in Leubner's method for lipase, or to 60 units in Somogyi's (7) method for the estimation of plasma amylase.

Firstly, normal children were studied to observe normal conditions. 40 children served for controls, and in more than half of these, several examinations were made of each child on different days, partly with tubing alone, partly with secretin. I do not want to go into details, but the striking fact has to be mentioned that, contrary to the observations of several authors, the output of enzymes is fairly uniform in each individual and concentrations below normal were never found in healthy and normally developing children. As to their response to different stimulants, especially secretin, and to the parallel concentrations of the three enzymes, the findings fully corresponded with the observations made on animals by Babkin (8), Anrep, Lush and Palmer (9) and La Barre and Destrée (10) or on men by Lagerloef (11). Nevertheless, these conditions are quite different in pathological cases.

Pancreatic function in disease was studied on extensive material but of these I shall report only the findings of five groups (a) patients suffering from various non-intestinal infections (b) gastrointestinal diseases (c) atrophy and dehydration (d) toxicosis and (e) nutritional edema.

It was said that 100 per cent means the lowest limit of normal, but in the following only those were taken for pathological, whose enzyme values did not reach even 70 per cent.

(a) The first group consisted of 131 children who suffered from measles, diphtheria, scarlet fever, whooping cough and different infections of the respiratory tract. There were no cases of parotitis among them.

Measles and diphtheria did not seem to affect pancreatic secretion. No such inhibitory effects could be observed as were described by Racugno and Manca (12) and Pansini (13).

Scarlet fever, on the other hand, seems to occupy a special position. In the majority of cases, 25 out of 30, the output of enzymes was not normal. All of them were considerably increased in the first few days. This hyperfunction could be observed before the exanthem appeared. Then, from about the 5th day on, hypofunction appeared, especially of lipase. In some cases amylase was found normal and in a few, also trypsin. The dysfunction ceased at about the 20th day of the illness and at the beginning of the fourth week conditions were mostly found normal except in cases of serious complications. There was, for instance, one case that of a girl of 6 years, who developed nephritis on the 3rd day, mastoiditis on the 12th and pneumonia and septicemia on the 20th day. She died on the 29th day. On the third day, there was already a lack in lipase, while trypsin and amylase values were normal. But a week afterwards all the enzymes were lacking and the function of the pancreas was never reestablished.

There are, further, some quite special cases in which not only a dysfunction but a real inflammation of the pancreas occurs during scarlet fever. Similar cases have been reported by Goldie (14), Gülsow (15), Otto (16) and others. I could observe 2 such patients among the 30 examined. At first, only a very slight decrease was noted in the concentration of enzymes but unusually big amounts of juice could be aspirated. The values of serum amylase and lipase and urine amylase was very high at that time. In one of the children serum amylase was as much as 2 100 per cent. Conditions were the same on the 10th day. On the 15th, however, amylase only amounted to 56 per cent and lipase to 33 per cent in the serum while there were only traces of amylase and no lipase whatever found in the duodenum. The child, whose scarlet fever was only light, made a full recovery. But this is, in all probability, how cases of celiac syndrome due to secondary pancreatitis may originate (36).

In whooping cough and infections of the respiratory tract, including pneumonias, I could find no real dysfunctions, except

when toxicosis was associated with these diseases. In some chronic conditions, as in a case of empyema of 6 weeks' duration, lipase values of 15 and 25 per cent were found but those for amylase remained normal. I cannot confirm the common belief that there is pancreatic hypofunction with every pneumococcal infection.

So, the decrease in the output of enzymes during diseases is in no connection with fever and no parallelism could be found between pancreatic lesion and the severity of clinical symptoms. Another striking and constantly observed fact was that under pathological conditions there is no parallelism in the secretion of enzymes. Although this has been observed by quite a number of investigators examining human subjects, as Diamond and his coworkers (17), Lagerloef and his associates (18), Bykov (19), Cathala and al. (20), Chiray and Lebon (21), physiologists still clinging to the 40 year old supposition of parallelism, advanced by the school of Pavlov and then confirmed on human subjects by Wohlgemuth (22). As was said above, this phenomenon was only found to exist in healthy children.

(b) The second group consisted of 73 infants and children suffering from gastro-intestinal diseases such as various forms of gastritis, diarrhea, colitis, amebic and bacillary dysentery. Care was taken not to include cases in which other factors accompanying or complicating the diseases, would have influenced the activity of the pancreas.

The findings were generally uniform. Except in amebic colitis, the output of lipase was always low and especially so in bacillary dysentery. In severe cases no traces whatsoever of this enzyme could be found. The other two enzymes were seldom impaired but if so, rarely to such an extent as the fat splitting one. No dysfunction could be noticed in amebic processes except in one very severe case of colitis. (I, however, do not venture to state this as a rule as grave forms of amebiasis are rare in my country and so there has been opportunity of making enzyme determinations on 13 patients with amebiasis and of these only two presented dysenteric symptoms.)

In 9 cases of acute gastritis no lipase whatever could be found and only traces of trypsin and about 20 per cent of amylase. In

all the reexamined patients of this group, 36 subjects, the functions were restored to normal within a few days after stormy symptoms subsided. Pancreatic function did not seem to depend on special toxins, for there is no difference in the effects of the various *Shigella* strains.

(c) It has been frequently reported that atrophy and exsiccosis by themselves suffice to stop the function of the pancreas. (Kitai-gorodskaja (23), Frenkel (24), Greiner (25), De Villa (26). I cannot support this statement in such a form. I examined 11 cases of atrophy due to under nourishment through food of adequate quality and, with the exception of one child, not only was there no dysfunction to be found but 3 of them showed quite unusually high concentrations of all three enzymes, especially trypsin. In one of them the value of this enzyme reached 1450 per cent.

The situation is rather similar in those dehydrated children in whom the loss of fluid is neither dependent nor accompanied by conditions causing pancreatic dysfunction. Among 12 cases with or without loss of salt, there was a baby of 8 months who gave values of 1 100 per cent for lipase and 1 400 and 1 700 per cent for trypsin and amylase. The fluid output of the pancreas was, however, found to be extremely diminished as no more than 2 ml of thick juice could be aspirated in 40 minutes. The pancreas seems to respond to thirst just as the other salivary glands.

It is interesting to record the response to secretin. A few minutes after an intravenous injection there was an output of 5 ml in the first 5 minutes and 6 ml in the second. The concentration of enzymes fell at once to 200 per cent, 400 and 420 per cent in the first portion and to 90 per cent, 90 and 70 per cent in the second. Similar results were obtained in the other members of this group. This seems, at least in infants, to be direct evidence in favor of Mellanby's (27) theory, that secretin is responsible for the secretion of fluid but not for that of enzymes. At the same time, it is in contrast with the observations of many authors, who all reported that there is pancreatic failure in atrophy and exsiccosis. I think that this contradiction has two causes. As these investigators used only one tube, the small amounts of pancreatic juice may have been lost. Or, the subjects observed were not simply

dehydrated but suffered from other conditions, as, for instance, toxicosis.

(d) The almost complete lack of secretory function in toxicosis is a constant finding of all investigators. (Freudenberg and Brühl (28), Gross (29), Hess (30), Macciotta (31), Philipsborn (32). In the 19 infants examined by me, there was not one whose pancreatic activity was not impaired to a considerable degree. There were no means of observing when the dysfunction begins but it ceases as soon as the toxic symptoms disappear. It is unknown which factor inhibits the activity but it is certainly neither the circulatory one nor acidosis.

It seems to me that the importance of this dysfunction in toxicosis has not been sufficiently strongly emphasized. Although even a complete lack of pancreatic enzymes does not mean a total insufficiency of fat digestion, such patients, however, always excrete 40 to 50 per cent of the fat taken in. This further aggravates the diarrhea already existing and precipitates the loss of minerals and water. Naturally, the vicious circle is of the greatest significance in those cases in which the condition giving rise to toxicosis exerts, at the same time, an inhibitory effect on the pancreas. It may, therefore, be assumed, that this is one of the causes why bacillary dysentery, for example, so often leads to toxicosis.

(e) The last group was that of 35 infants suffering from nutritional edema. Care was taken not to include patients in whom some condition other than deficiency of adequate nourishment was the cause of edema.

The first symptoms at a time when there is still no change in the blood proteins, are slight loss of weight and diminution and then the ceasing of the output of pancreatic enzymes. The first to diminish and then to disappear is the fat splitting one and the last the amylase. The concentration of enzymes in the blood is also considerably lowered. If milk could be given at this time, the condition improved at once. The pancreas began to secrete normally in two days and the infants recovered.

If, however, there was no milk available, edema appeared after a certain time. Most infants of this group already had edema when admitted. Of pancreatic enzymes, lipase was lacking in all,

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traces of trypsin could be found in some, and very small amounts of amylase (about 10 per cent) in the majority of children. There was no case with edema in which the enzymic would have been normal.

The condition could not be ameliorated by vitamins D or B₁ or nicotinic acid. B₂ complex or riboflavin alone seemed to make their state even worse and so had small amounts of milk. Adequate quantities, on the other hand, had a dramatic effect. The first sign of improvement was always the restoration of enzyme secretion, which mostly became normal within 3 days. Then the level of plasma albumen increased and the edema disappeared.

If the condition is not of long standing, the dysfunction of the pancreas ceases as soon as milk is given but returns if this is discontinued. After a certain time, however, there is no more response. In such cases the autopsy reveals not only scarring of the liver but also pancreatic fibrosis.

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The Prognosis of Amyotonia Congenita.

By **Sven Brandt.**

From the University of Aarhus, Pediatric Department, Denmark.

A follow-up of 75 cases diagnosed in Danish departments since 1900.

The existence of a benign congenital muscular hypotonia as described by Oppenheim in 1900 being still questioned by many authors, I have made a follow-up of all cases in Danish pediatric and neurologic departments diagnosed as Amyotonia congenita since 1904.

The material includes 75 cases of diagnosed or supposed Amyotonia Congenita. In addition the diagnosis of Progressive Spinal Muscular Atrophy of Werdnig-Hoffman has been made in another 39 cases 14 of which were paralysed from birth. Fig. 1 shows our more frequent tendency to make the last diagnoses through the last years instead of that of Amyotonia Congenita. The increased frequency of *all* cases may be explained from our wakening interest in these diseases.

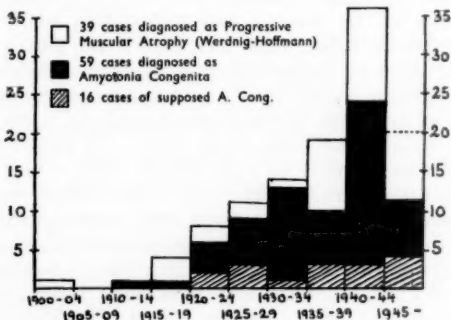


Fig. 1.

Of 75 cases, diagnosed as Amyotonia Congenita, 41 had died, all of them before 19 years of age and of these 56 per cent during their first year of life. (Fig. 2.)

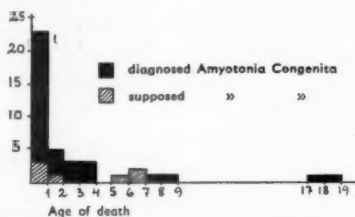


Fig. 2.

Only 34 of 75 patients were found alive. Of these 34 cases 14 may have been no cases of Amyotonia Congenita, the correct diagnosis made by the reexamination being as follows:

4 cases were not congenital. 3 of these were possibly cases of ricketts with pronounced muscular weakness.

2 cases were cases of spastic diplegia, thus demonstrating an interesting changing from the atonic type into the typical picture of spastic diplegia without any hypotonia left.

2 were cases of Congenital Cerebellar Ataxia.

1 case were probably a case of poliomyelitis.

5 children were feeble-minded, 3 being in asylums for imbeciles.

Of the remaining 20 cases 4 had been observed only few months and no exact prognosis could be made at the present time.

7 were markedly invalides, progressive spinal atrophy being the correct diagnose.

In 2 cases, now 8 years old, no progression had been observed and the children were only little invalides.

Complete or practically complete restitution was observed in 7 cases. The eldest being now 21 years of age. The hypotonia at birth was of different degrees. One girl, complete atonic for several months, had completely recovered, quite spontaneously, at the age of 9 months.

In details these cases will be published later.

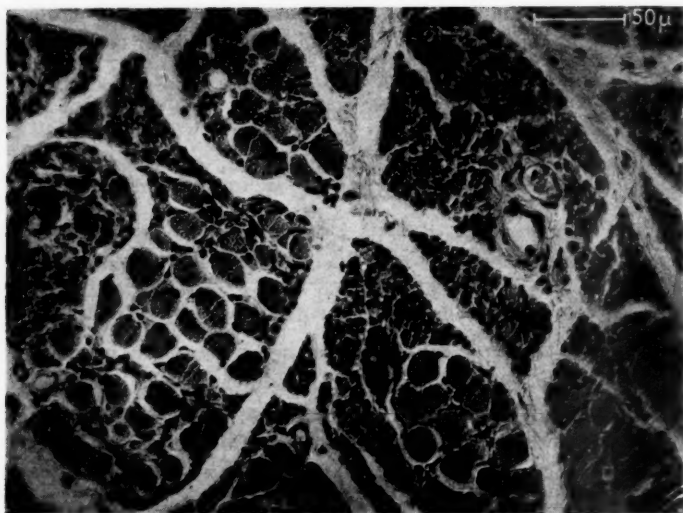


Fig. 3.

The result of my investigation has been the statement that benign cases of congenital muscular weakness with complete restitution of even markedly hypotonia may really occur, less often, however, than supposed by Oppenheim, many cases getting that diagnoses being cases of Werdnig-Hoffmann's disease.

A distinction from other types of weakness of the muscular system during the first months of age may be difficult or impossible without a convenient time of observation or without an exact neurologic examination. In this must be included a histological examination of muscular biopsy, the last slide showing the typical picture of spinal atrophy, characteristically for the malign types, not really deserving the name of Oppenheims amyotonia. The correct diagnosis in such cases must be Congenital spinal muscular atrophy.

The etiological entity of Oppenheim's disease may be questioned. Probably the weakness may be of different causes.

Plenary Session—Tuberculosis.

RELATOR.

Anti-Tuberculosis Vaccination and its Significance in Prophylaxis against Tuberculosis.

By **Arvid J. Wallgren**, M. D., Stockholm, Sweden.

The fact that a specific immunity against new tuberculous infection develops after a primary tuberculosis has many times been proved by experimentation on animals. A good many physicians, however, incline to falter when it comes to applying this experience to the human organism. There may be agreement about the fact that infection produces an immunity in the human organism; yet little or no value is attributed to this immunity as a protective factor.

One reason for this attitude is that nonspecific natural resistance usually is dominant, and that this is the decisive factor in determining the course of tuberculosis. This nonspecific resistance is so important in comparison with specific immunity that the latter is believed to be negligible. While the nonspecific protective factors control the total tuberculous process after infection and in general decide the fate of the tuberculous individual, the protective effect of specific tuberculous immunity is thus thought to be limited to counteracting new exogenous infections.

At the same time, certain authors deny this effect of specific immunity, maintaining that an individual after having survived a primary infection is less liable to tuberculous infection than an uninfected one only because of the strong natural resistance which existed before the first infection and which prevented progressive disease. However, it must be remembered that natural resistance changes considerably during the various periods

of human life, that it can be diminished under certain circumstances, and that at such times it is of great value if lessened natural resistance is increased by specific immunity.

Another reason why a specific immunity to tuberculosis is often considered to be valueless is the fact that it cannot prevent late postprimary tuberculous disease. The fact is well known that in spite of existing immunity, tuberculous osteomyelitis and arthritis or phthisis may develop. A very pessimistic conception of immunity will result if its value is judged only by its ability to prevent postprimary disease. Specific immunity cannot prevent these diseases to the same extent that it can obviate the direct consequences of an exogenous superinfection. So-called endogenous re-infection can be much more intense than exogenous infection, and may cause a change in specific immunity. Furthermore, tuberculous immunity, like immunity after any contagious disease — for instance, syphilis — is directed exclusively or chiefly against new infections from outside. Usually it can prevent exogenous superinfection from causing new primary complexes. Judging from experimental studies on animals, this is achieved by slowing the multiplication and dissemination of the superinfecting bacilli.

A third argument against the importance of specific tuberculous immunity is based on the observation that in animal experiments the immunity is only relative and can be overcome by large re-infections. However, specific immunity is valuable because superinfection is seldom so strong that the immunity is overcome. Aerogenous infection is caused only by minute cough droplets which contain a minimal number of tubercle bacilli and which remain suspended in the air. During inhalation these droplets, as well as dust infected with tubercle bacilli, meet many obstacles on their way to the lungs. Aerogenous contamination almost always causes a minimal infection, and the relative tuberculous immunity is usually sufficient to combat it. In the case of an enterogenous infection, on the other hand, a much larger dose of bacilli is necessary for infection because of the very strong nonspecific resistance of the organism against this kind of contamination. The protective effect of specific immunity combines

with natural resistance, and together these defensive factors usually are able to prevent fresh exogenous infections. Therefore the immunity resulting from a well healed tuberculous infection, even though it be only relative, seems in an extraordinary way to protect against the immediate consequences of new infections from without.

The value of specific immunity thus is limited. In spite of this limitation, we consider the possession of a specific tuberculous immunity to be of advantage for the individual. Almost every day the importance of this fact is demonstrated. Pediatricians especially have the opportunity to observe how tuberculin-positive children are exposed to tuberculous infection without any consequences, whereas tuberculin-negative children often develop primary tuberculosis. In an individual with an old tuberculous primary complex we never see another primary tuberculosis. Therefore, it would seem as if an immune individual need have no fear of contact with infectious tuberculous persons.

I have dwelt on these problems of the value of immunity so extensively because in the prophylaxis of tuberculosis all methods of vaccination depend on specific immunity and because there are physicians who deny this and who question whether vaccinations should be done.

We believe that a person who has survived a tuberculous infection has in certain ways an advantage over individuals who still are uninfected. But there is no doubt about the fact that in other ways an infected individual with tuberculosis is in a more disadvantageous position than one who has escaped infection. In his body he is harboring tuberculous foci from which, in case of a variation in natural resistance, tubercle bacilli may escape and cause postprimary tuberculous disease. In the case of a virulent infection, therefore, the advantage of the possession of an immunity caused by the infection is acquired simultaneously with the risk of developing serious tuberculous disease during the formation of immunity or later on. Since we cannot evaluate the possibility of this chance in an individual case, it would be absurd to produce deliberately a virulent infection in order to bring about an immunity protecting against further virulent in-

fections. It is the object of vaccination to produce an immunity without risk to the individual, by securing the same kind of protection that is obtained with a natural infection without simultaneously endangering the individual's health.

Ever since it was shown by experimental studies on animals that tuberculous infections leave behind them a specific immunity against tuberculosis, interest has been concentrated in many places on the generation of immunity without any damage to the individual. Many different methods have been used. Attempts were made to eliminate the dangers of a virulent infection by making the artificial infection as small as possible; attempts were also made to produce immunity by means of vaccine from dead tubercle bacilli. Both of these methods are now of only historical interest, the former being abandoned because of its great dangers, the latter because the immunity obtained was insufficient.

Attention was then paid to the attempt to produce a vaccine from non-pathogenic but living tubercle bacilli. To this group belong Friedmann's turtle bacillus vaccine, Behring's Bovo-vaccine, Calmette and Guérin's BCG vaccine and finally the vaccine produced from the Wells vole bacillus. The two first-named have been completely abandoned. The vole vaccine has not yet been tested sufficiently on human beings. The BCG vaccine is the only one which has been so widely used that its value can be estimated.

A prerequisite for the use of BCG vaccine is its harmlessness. Wide experience from all over the world shows that BCG bacilli cannot cause progressive tuberculous disease, either in man or in the usual laboratory animals. There have been many discussions about this question, and since everyone now seems to agree that BCG vaccine is innocuous, I think it unnecessary to discuss this point further.

In their vaccination experiments Calmette and his co-workers gave large doses of BCG by mouth to newborn infants. Tuberculin tests proved that the proportion of subjects who became tuberculin-positive by this method of vaccination remained small, and those who did so developed their positive reactions very late. Therefore, there was no proof that the vaccination

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had been successful. Nowadays the vaccine is principally given parenterally with adequate dosage.

The choice of the method of parenteral vaccination, the local and general reaction after vaccination, the adequate dose, the degree and duration of the immunity — all these are questions that are still being discussed and have given rise to quite an extensive literature. It is my intention to take up other questions which, in my opinion, are more important; and I shall dwell chiefly on the theoretical and real objections to vaccination, its immunizing effect, and its value in the prevention of tuberculosis.

The introduction of the intracutaneous method of vaccination, in place of the peroral one recommended by Calmette, was motivated in part by the desire to administer exact doses of the vaccine. This method of vaccination was moreover chosen in order to avoid the large abscesses resulting from experiments with subcutaneous injections in France. The vaccine was shown to produce sensitivity to tuberculin in laboratory animals, and there was also evidence to support the belief that vaccination in man would cause allergy to tuberculin. By the intracutaneous method the vaccine could therefore be administered in exact dosage, and after a certain period tuberculin sensitivity would appear without causing any severe local reactions.

The emphasis on tuberculin sensitivity after vaccination is not based upon the conviction that tuberculin sensitivity and immunity are identical terms. The endeavor to develop tuberculin sensitivity by means of vaccination is motivated by the fact that this is the only way to prove easily that the organism has reacted to vaccination, not only locally but also generally. In practice the vaccinated individual is considered to have acquired immunity after he has become tuberculin-sensitive, and it is believed that the immunity lasts at least as long as the tuberculin sensitivity.

A tuberculin test is usually performed 6 to 8 weeks after vaccination because sensitivity generally becomes manifest at this time. Resistance against BCG varies in different individuals. Young infants exhibit an especially mild reaction to BCG, as they do to variola vaccine, and for them a double quantity of

BCG vaccine or even more is necessary in order to obtain tuberculin sensitivity.

Sometimes the local focus is insignificant, and sensitivity to tuberculin does not appear after the usual interval. In these cases the vaccination is repeated and often larger doses are used, and usually sensitivity is attained after one or more re-vaccinations. In exceptional cases, especially in infants, the general reaction fails to manifest itself as sensitivity to tuberculin although there is a distinct local focus.

This gives rise to the question whether the vaccination was of any use in such a subject. The possibility can hardly be denied that there may occasionally be found individuals who cannot react to tuberculin after BCG, regardless of the fact that vaccination provides them with the desired immunity. As is known, there are rare cases of tuberculous disease where, in spite of proof of the specific disease, there is no tuberculin reaction, however large the administered dose of tuberculin may be. This seems to occur more often after an avirulent infection, like the one with BCG.

BCG vaccination should be performed in such a way that the focus of inoculation causes as little inconvenience as possible. As has been just mentioned, this is the reason why we chose the intracutaneous method instead of the subcutaneous one for the injections. The local reaction after intracutaneous vaccination remains superficial and usually of slight extent, and in case of ulceration there will result only a superficial sore which heals faster than the abscesses caused by subcutaneous injection. Very slight ulceration occurs quite often but is of no significance and often fails to be noted by the vaccinated person. Larger abscesses which take from 4 to 8 weeks to heal are very rare, are seldom troublesome, and usually heal spontaneously. The individual factor doubtless is of great importance in the behavior of the local vaccination focus. Certain individuals are more sensitive to BCG bacilli than others. Unfortunately, it is impossible to decide beforehand who is hypersensitive to BCG, and one must therefore always reckon with the risk that the local lesion will become too large. If the vaccination was carried out correctly, it is probable

that in such cases there is very little resistance against BCG. Since BCG is composed of modified tubercle bacilli, the conclusion seems to be justified that the individual also possesses very little resistance against virulent infection. In such cases an acquired immunity to tuberculosis is, of course, of still greater value than in other cases where the nonspecific resistance to a certain degree can substitute for a lack of specific immunity. Without this specific immunity of the vaccinated, the risk might have been greater that a virulent primary infection later on would cause progressive tuberculosis.

In order to avoid abscesses sometimes originating from parenteral injection of the vaccine, a new method of vaccination was introduced in France about 5 years ago: cutaneous vaccination. Negre and Bretey proved that guinea-pigs after BCG vaccination by scarification became tuberculin-positive and possessed stronger resistance against small doses of virulent tubercle bacilli than unvaccinated animals. Rosenthal applied multiple punctures in the skin instead of scarification, and claimed that by this method local reactions are avoided, that scarring and supuration of the regional glands do not occur. Rosenthal stresses the fact that this type of vaccination is easily performed and therefore is adaptable for more general use.

Birkhaug has become a devoted student of the Rosenthal method, which he developed further. Originally the method was carried out by administering 30 to 40 punctures with the point of a slender needle through a drop of concentrated vaccine. This procedure required a long time and was not adapted to mass vaccination. Birkhaug then constructed a comb-like device with a series of parallel needle-points, by which a great number of punctures on the skin could be made simultaneously. A further improvement of the apparatus is a kind of spring lancet. By cocking the spring of the lancet and discharging it against the skin, 40 sharp needle points pierce the superficial layer of the skin. In order to accelerate the whole procedure of vaccination, Birkhaug uses a piece of silk paper soaked in BCG vaccine, against which he presses the apparatus during vaccination instead of applying a drop of vaccine on the skin. As they penetrate the silk paper

the needles introduce vaccine into the skin. After 2 minutes of drying the paper is removed. The method appears to be simple, practical, and easy to carry out. Birkhaug, on the basis of extensive experience, figures that he can perform from 2 to 3 vaccinations per minute.

Birkhaug states that by means of his apparatus he vaccinated 307 tuberculin-negative school-children. In 42 of them (13.7 per cent) no reaction appeared on the skin, nor did they show a reaction to tuberculin. In each of the remaining 264 pupils there appeared a more or less manifest primary lesion at the site of each needlepoint vaccination, and 97.3 per cent of the children became tuberculin-positive. Thus, 83.6 per cent of the total vaccinated group exhibited a positive reaction. Birkhaug states furthermore that in 3 per cent he observed pustules in the cases where this vaccine (20 mg per cc) was used. Since the spring of 1944 Birkhaug has increased the concentration of the vaccine for cutaneous use to 50 mg per cc in order to improve his results. With this stronger vaccine he obtains tuberculin sensitivity in all cases after 2 months, but 9 per cent of the vaccinated have developed draining pustules which did not heal until after 5 or 6 weeks.

It would seem worthwhile to make further comparisons between the method of cutaneous vaccination with scarification or multiple punctures and the intracutaneous method. This should be done under conditions which allow each case to be controlled in an attempt to find out the most satisfactory concentration of BCG suspension for these methods, the best way to carry out the vaccination, the number of tuberculin-positive persons after vaccination, and the duration of tuberculin sensitivity. Vaccination by means of a vaccination spring lancet, as performed by Birkhaug, appears to be excellent, but only a few might develop the technique which gives him such swiftness in mass vaccinations. Moreover, here the problem arises of sterilization of the apparatus between vaccinations.

Lind has to a small extent tried the intracutaneous method and the methods with scarification and multiple punctures on newborn infants (150 in each group). From 7 to 10 weeks later, tuberculin testing proved that 38 per cent had become positive

after vaccination by the puncture method, 50 per cent after scarification (concentrated vaccine), and 86—95 per cent after intracutaneous vaccination (with doses of 0.05—0.10 mg BCG). It may be stressed that this result was obtained on young infants, whose capacity to react to BCG is decidedly less than that of older children and adults. This circumstance might explain the not very encouraging results of the scarification and puncture methods.

Who should be vaccinated? In point of principle, every tuberculin-positive person will profit from an additional increase of his resistance against tuberculosis as may be obtained from BCG vaccination. Yet certain groups are in greater need of it than others. We believe that all persons who live or who are going to live in tuberculous surroundings should be vaccinated if they are tuberculin-negative. This applies to children as well as to adolescents and adults. Even more important is the protection of vaccination for certain persons whose natural nonspecific resistance against tuberculosis for some reason or other is low.

The earlier a Calmette vaccination is carried out, the better it will be for the child. Usually it is impossible to decide beforehand when the child may be exposed to the risk of infection. Thus it would be best to vaccinate in the newborn period, a procedure often carried out and especially easily done while the infant is in the maternity hospital. The newborn infant's low capacity to react to BCG vaccine is a disadvantage. Even if considerably larger doses of vaccine are used than are customary, the vaccination often does not lead to rapid tuberculin sensitivity.

At Infant Welfare Centers it is possible to establish contact with the child soon after birth for the purpose of vaccination. If the physician is interested in this prophylactic measure, he will in most cases succeed in obtaining the parents' consent. Hardly any objections to vaccination are encountered in a Swedish Infant Welfare Center.

School age is another convenient period for vaccination of tuberculin-negative children, and vaccination as well as follow-up for tuberculin control is easily carried out at this time. Propaganda for BCG prophylaxis should be instituted most intensively

when children are finishing school, at the age of 14 or 15 years. At that time young adolescents seem to be especially susceptible to tuberculosis. Moreover, the danger of infection at this age is usually increased by the change of living conditions and surroundings, when young people leave the protection of their home in order to obtain professional training or to continue their studies, and thus they will be exposed to more or less uncontrollable contact with other people. At this age, therefore, prophylaxis against tuberculosis is most necessary.

The question of the duration of immunity is of utmost importance for the evaluation of BCG vaccination in the fight against tuberculosis. The immunity should last until the vaccinated individual becomes infected with virulent tubercle bacilli. Then, as a rule, the transient and weaker artificial immunity imperceptibly merges into the stronger and usually life-long immunity caused by a virulent infection. The BCG immunity then has accomplished its purpose. In Sweden we have had a 20-year experience with BCG vaccination, and it would seem that within this period definite information should have been gathered regarding the duration of immunity. This, however, is not the case. Relatively few attempts have been made to elucidate this problem. In fact, the task is admittedly a difficult one. It is hardly possible to gather material which is scientifically unobjectionable because of the uncertainty of exclusion of virulent tuberculous infection after vaccination in any single case.

According to previous experience, virulent superinfections generally occur in BCG vaccinated and BCG immune individuals without symptoms. If in a BCG vaccinated person tuberculin sensitivity is proved a good many years after vaccination, this sensitivity might be due to a virulent infection and is not necessarily caused by BCG. Most BCG vaccinated people live under such conditions that the possibility of virulent infection cannot be excluded with certainty. In order to eliminate this factor in the study of the duration of BCG immunity, the group should consist of individuals undergoing a long period of treatment where the personnel and the patients are under constant control and where there is no further contact with infectious tuberculosis.

Insane asylums and schools for the blind might be available for this purpose.

Previous experience has shown that the duration of tuberculin sensitivity varies from case to case and that it can never be determined beforehand. Investigations made by Törnell indicate that persons who had a very strong reaction after vaccination have kept their tuberculin sensitivity for a longer time. Likewise, it has been shown that persons with a very strong local reaction to vaccination tend to acquire tuberculin sensitivity more rapidly. A study made by Anderson and Belfrage in Gothenburg gives valuable evidence on the duration of BCG immunity. In 1938 they tested the tuberculin sensitivity of all subjects vaccinated with BCG since 1927, a total of 858 persons. They divided the cases into 3 groups according to the risk of virulent infection after vaccination: in the first group individuals were included who had lived in tuberculous surroundings; in the second group, those who had lived in surroundings free from infection; and in the third group, those for whom the possibility of infection could not be excluded. Anderson and Belfrage found that the frequency of tuberculin sensitivity within the three groups was the same, that is, 96 or 97 per cent, a result which they considered to indicate that tuberculin sensitivity within the non-exposed group, in which it should have been produced exclusively by BCG, had persisted after vaccination — in certain cases, up to 10 years. This would seem to indicate that artificial immunity can persist for ten years and possibly longer in favorable cases.

Even if BCG immunity can last for ten years, it would seem proper and cautious to assume that in an individual case it might be considerably shorter and that a tuberculin test is the only sure way to demonstrate its persistence. Such tuberculin control should not be omitted if BCG immunity is expected to be of help until a virulent infection has occurred. This may happen many years after vaccination. It is, however, of utmost importance that tuberculin sensitivity be confirmed by skin test during the ages of greatest susceptibility for the development of tuberculosis — the years of infancy and adolescence. This can be done

at certain intervals at Infant Welfare Centers and at schools, for instance at the ages of 3, 7 and 15 years.

Occasionally cases of tuberculosis are reported in persons who had been vaccinated with BCG. There is nothing remarkable in this fact, and as long as these cases remain relatively uncommon, such observations will not detract from the value of vaccination. No immunity to tuberculosis is absolute, and it would be definitely wrong to expect a 100 per cent protection from BCG immunity. BCG immunity not only is weaker than the immunity which follows virulent infection but is also more transient. Tuberculous disease developing in an individual previously vaccinated with BCG does not necessarily mean that clinical tuberculosis has appeared in a BCG immune person. The immunity following vaccination may have disappeared before the virulent infection was acquired, in which circumstances, of course, the vaccination could not provide any protection. Before it can be stated that in a given case there has occurred a variation in BCG immunity, it must be proved that the patient had been continuously tuberculin-positive before falling ill. Every once in a while the observation is made that tuberculous disease appears in an individual who undoubtedly still had some BCG immunity.

BCG immunity offers as little protection as does the immunity generated after a virulent infection, so far as post-primary diseases such as tuberculosis of bones, genito-urinary tuberculosis, or tertiary tuberculosis of the lungs is concerned. If a BCG vaccinated person is infected with virulent bacilli and, because of his immunity, fails to come down with a clinical primary tuberculosis, he may harbor virulent bacilli in his body, and these are very likely later on to behave as if the individual had not been vaccinated. This means that the bacilli, in the event of a variation in the natural resistance for whatever reason, can be the cause of post-primary disease. There are some case reports of post-primary tuberculous disease after BCG vaccination. The number of these cases, however, is strikingly small in comparison with the number of BCG vaccinated individuals, which may in-

dicate that BCG immunity protects to a certain extent against post-primary diseases.

It seems likely that by means of Calmette vaccination one kind of post-primary pulmonary tuberculosis can be prevented to a certain degree. I refer to the type of progressive pulmonary tuberculosis which, especially in adolescents, starts from a fresh primary tuberculous focus in the lungs; the primary tuberculosis apparently develops directly into phthisis. Such a process seems to occur more often in cases where the primary tuberculous lesions in the lungs are relatively large than in cases where they are minimal. If BCG vaccination can prevent the development of a severe primary tuberculosis in the lungs, it should also be able to provide some protection against this change into progressive pulmonary tuberculosis.

A large proportion of the tuberculous diseases reported after BCG vaccination — especially primary tuberculosis — are explained not by a failing BCG immunity but by the appearance of the infection before the development of the immunity. BCG vaccination performed during the incubation period of a virulent tuberculous infection has no protective value. If a virulent infection occurs before BCG immunity has developed, no value is to be expected from vaccination.

Attempts that have been made to assess the protective effect of BCG vaccine by means of a long-term systematic study of large series of cases are of greater value than are single case reports of tuberculous disease following vaccination. There are a good many such comprehensive investigations, most of them being of older date, others more recent. I shall refer only briefly to some of the latter. On the whole, none of these investigations has produced material for a direct comparison of a vaccinated with a non-vaccinated group. As more people become vaccinated it will become more difficult to assemble an adequate control group. An ideal plan would be to vaccinate with BCG, without selection, every second individual of a group of tuberculin-negative people living in the same surroundings, and then to follow these two groups after exposure to the same risk of infection. At present there is either practically no control group at all, or it

is too small in proportion to the size of the vaccinated group, or the control group is chosen from another period.

Göteborg was the first Swedish community in which routine BCG vaccination was introduced for a certain population group — namely, all infants from surroundings known to be tuberculous. This was begun in 1927. A comparison of the mortality statistics of tuberculosis among infants before and after BCG vaccination was introduced shows a most remarkable decline. The general mortality had, as a matter of fact, also decreased during this period, but not in the same proportion, which means that the rapid decline of the infant mortality rate cannot be explained by this circumstance. I should like to add that none of the infants who died from tuberculosis had been vaccinated with BCG. A re-examination, including x-ray, carried out in 1934 showed that among the 230 infants who after vaccination between 1927 and 1933 had lived in contagious surroundings, only one acquired an evident primary tuberculosis, and that none died from tuberculosis.

The re-examination of all the individuals vaccinated in Göteborg, previously referred to as having been carried out by Anderson and Belfrage in 1938 and 1939, demonstrated that only 3 out of 858 individuals had fallen ill with tuberculosis — namely, with cervical adenitis, pleurisy, and erythema nodosum without involvement of the hilum — and that none had died from tuberculosis. On further re-examination, including x-rays, no case of tuberculous disease was found. Almost 400 of the vaccinated individuals lived in definitely infectious surroundings where they could hardly escape exposure. Unfortunately, this investigation lacks a sufficient control group of non-vaccinated persons. BCG vaccination was offered to all persons endangered by tuberculosis, and only some ten in all refused for various reasons to have vaccination carried out. Among those few cases, 3 died from tuberculosis. Out of 37 000 persons in Göteborg vaccinated with BCG before 1944, 6 cases of primary tuberculosis occurred, 11 of pleurisy, and 6 of pulmonary tuberculosis.

From the nursing school at Sophiahemmet, Nordwall published in 1944 an investigation on the effect of BCG vaccination

among the pupils of the school. Since 1935 a total of 205 tuberculin-negative pupils had been vaccinated with BCG by the intracutaneous method customarily used in Sweden. At the time of re-examination the vaccination had in 162 cases occurred one or more years before, and 94 had been under observation for more than 3 years. The usual x-ray controls were negative except in one instance in which primary tuberculosis was suspected. Nordwall's control material consists of student nurses from a period before vaccination had been introduced. This is, of course, no adequate control group, since the conditions for exposure might have been quite different at that time. Among the 50 pupils who at the beginning of the course in 1932-1935 were tuberculin-negative and were not vaccinated with BCG, tuberculous disease occurred in 20 cases, or 40 per cent: Pulmonary tuberculosis developed in 4 and meningitis in one case, while the rest had primary tuberculosis or pleurisy. Nordwall finishes his account with the following words: "Tuberculosis, which before the introduction of BCG vaccination was a permanent menace to the tuberculin-negative pupils and which caused the management of the school many serious worries, now has ceased to be a problem."

The military surgeon, General Lindsjö, who introduced voluntary BCG vaccination of tuberculin-negative conscripts in 1939, has reported results up to 1942. Of 15 000 BCG-vaccinated draftees who were followed, 4 had acquired primary tuberculosis and 5 pleurisy. There was no control group of non-vaccinated persons for the same period.

A recent experience in one company of a Swedish provincial regiment illustrates the possible dangers of exposing tuberculin-negative non-vaccinated conscripts to tuberculous infection. Among the 141 men of the company, 88 were tuberculin-negative at the time they entered the camp, i. e., 62 per cent. During service one of the tuberculin-positive recruits fell ill with pulmonary tuberculosis. The disease was not recognized in time, and this man thus happened to become a very dangerous source of infection for his comrades. In the course of a few months, after his pulmonary tuberculosis had become manifest, one after the other, 28 of his tuberculin-negative comrades came down with

primary tuberculous lesions in the lungs or with pleurisy. Three cases developed miliary tuberculosis with fatal outcome. A second tuberculin test of the surviving originally tuberculin-negative draftees showed that only one of them was still negative, while all the others were infected with tuberculosis. In spite of the military physicians' propaganda for vaccination, none of the recruits of this company had wanted to be vaccinated with BCG.

H. Chr. Olsen, physician of the Department for Tuberculosis at Rønne, in 1945 kindly informed me of an interesting observation regarding the incidence of tuberculosis in Bornholm after the introduction of BCG vaccination. Among Bornholm's 46 000 inhabitants, about 10 000 — mainly school children, adolescents and young adults — had been vaccinated since 1941: The distribution of recently reported cases of tuberculosis among the different age groups shows a disappearance of the peak for the age group 15 to 35 years which had been present before the introduction of vaccination. Olsen rightly correlates this change with the circumstance that a larger proportion of the population within this age group has become less susceptible to tuberculosis because of an acquired BCG immunity.

The Danish physician Tage Hyge reported the consequences of an infection with tuberculosis in a school of girls 12 to 18 years old. He divided them into 3 groups: 1) 130 who had become tuberculin-positive after primary infections; of these, 105 were exposed to reinfection, and 2 of them came down with a mild pulmonary tuberculosis during the three years following the epidemic of tuberculosis. 2) 133 BCG-vaccinated and tuberculin-positive individuals, of whom 106 were exposed to reinfection, 2 of them contracting progressive pulmonary tuberculosis within the following three years and requiring treatment by pneumothorax. 3) 105 tuberculin-negative individuals, of whom 94 were exposed to infection; 70 became tuberculin-positive, and of these 41 came down with tuberculosis which in 6 cases developed into progressive phthisis, with one death. The remaining 35 cases healed. Hyge calculates the tuberculosis morbidity rates as 1.9, 1.9 and 56.6 per cent for the respective groups.

An adequately made study is that by Aronson and Palmer in

the U. S. A. In 1935—1938 they vaccinated 1 550 tuberculin-negative Indians aged 1—20 living in reservations or in some communities of Alaska. As a control group they injected salt solution in 1457 tuberculin-negative Indians from the same places and of the same ages. Annual follow-up examinations showed that the two groups were exposed to virulent infection to the same extent. Four vaccinated Indians and twenty-eight of the non-vaccinated had died from tuberculosis. On further comparison of the test vs. control groups, minimal tuberculosis developed in 8 vs. 20 cases, moderately or advanced pulmonary and extra-pulmonary tuberculosis in 9 vs. 48, pleural effusion in 4 vs. 18, enlarged hilar glands in 19 vs. 99, parenchymal lesions in 11 vs. 74. The total incidence of tuberculous disease was 40 in the vaccinated group and 185 in the non-vaccinated.

Ferguson of Saskatchewan has made an interesting observation on the incidence of tuberculous disease among nurses and sanatorium employees in 1934—1943. Out of the 1 005 BCG vaccinated nurses in general hospitals 9 acquired tuberculosis (= 0.9 per cent). Of the 759 non-vaccinated tuberculin-negative nurses the tuberculosis incidence was 29 (= 3.8 per cent) — that is, about four times as high a tuberculosis rate in the non-vaccinated group. This difference between the two groups was still more pronounced among graduate nurses and nurse assistants in sanatoriums: 203 vaccinated with 5 cases of tuberculosis (= 2.7 per cent), 113 non-vaccinated with 18 cases of tuberculosis (= 15.9 per cent). I should like to quote Ferguson's conclusion: "The serious situation that had been developing with regard to excessive incidence of tuberculosis among nurses and sanatorium employees who did not react to tuberculin on entering the environment, during the period 1930 to 1938, has not been present since vaccination of negative reactors was begun in September, 1938. The nursing schools and the League in Saskatchewan no longer have anxiety and worry with regard to excessive tuberculosis developing among their negatively reacting staff."

So far as I know, there is only one report of an attempt to prove experimentally in man the immunizing effect of BCG vac-

cination. It was carried out at the University Children's Clinic in Vienna and was reported by Türk. Two mentally retarded infants, 4 and 14 months old, both badly injured by birth trauma, were vaccinated with BCG and became tuberculin sensitive. A few months afterwards both were infected with virulent tubercle bacilli by means of scarification of the skin. Simultaneously a third child of 19 months, also affected by birth trauma, was similarly infected as a control. The last infant developed a typical tuberculous primary complex with ulceration of the site of scarification and with enlargement and suppuration of the regional lymph nodes. The ulcer healed after 6 months; the fistulous nodes only began to heal 8 months after the infection. The two vaccinated infants exhibited no reaction at all to the virulent bacilli.

Calmette stated that the virulence of BCG would remain unchanged. This is no longer believed to be true, and it is known that other live vaccines — e. g., variola virus — may change in virulence. In the years immediately following 1920 a number of reports were published to the effect that BCG regained some of its original virulence under certain conditions of cultivation or by animal passage (Watson, Petroff, Gerlach, Dreyer and Wolium). Petroff's investigations in particular aroused considerable attention. However, during the last ten years reports of increase in virulence of BCG are lacking. The organisms seem, in fact, to have become less virulent than in the beginning. While Petroff did not at first experience any difficulty in establishing an increase of virulence in cultures, the same experiment with cultures obtained later from the Pasteur Institute was not successful.

Certain recent reports from Norway state that it has become more and more difficult to render vaccinated individuals tuberculin-positive. I may recall the fact that Birkhaug was forced to make the vaccine used for the cutaneous method ten times more concentrated than at first. A diminution in virulence of the BCG culture employed in Norway may constitute the only plausible explanation. No evident decrease of the strength of the Swedish vaccine has been observed. Yet it is not impossible

that BCG may eventually become so avirulent that it no longer produces any reaction. Because of this possibility it may prove to be a great advantage that we have now gained access to another type of tubercle bacillus which has not been made avirulent artificially but which seems to possess a natural virulence suitable for vaccination. These tubercle bacilli originate from England (Wells), where they were cultivated from a species of vole in which the bacilli caused epidemics of tuberculosis. These so-called vole bacilli are avirulent for guinea pigs and man. In experiments with guinea pigs they produce a degree of immunization and tuberculin allergy which seems equal to that produced by BCG. In our country this vaccine has been tried to only a slight extent in man. When used in the same quantity as BCG, it produced a insignificant lesion after intracutaneous vaccination and evoked a tuberculin sensitivity which appeared earlier than after BCG (Olin, Wahlgren and Widström). Therefore, I believe it likely that we can use vole bacilli as a substitute for BCG if the vaccination effect of the latter diminishes. However, at the present time no more can be said about the vole vaccine than that it is innocuous, that it produces tuberculin sensitivity, and that in animal experiments it has proved to have a good immunizing effect.

Precautionary methods against tuberculosis have led to a shifting of the first tuberculous infection from childhood to adult age. As a consequence, more people acquire their first infection during adolescence or adult life. The Calmette vaccination, as carried out in Sweden, apparently is succeeding satisfactorily in diminishing the risk of the immediate consequences of tuberculous infections, and therefore helps overcome the disadvantages of an individual who was not immunized by a primary infection during childhood. The Calmette vaccination therefore fills a gap in the fight against tuberculosis and must be regarded as a valuable complement for rational anti-tuberculosis work. So long as there are ambulant patients spreading the disease, and until we obtain a more effective method, BCG vaccination is likely to maintain its usefulness in prophylaxis against tuberculosis.

RELATOR.

Prophylaxis and Treatment of Tuberculosis in Children.

By K. Jonscher, Poznan, Poland.

Prophylaxis.

I. Increasing the resistance of the child's organism: All factors which contribute to improving the child's health, such as fresh air, appropriate diet and good general hygienic conditions, raise the resistance against tuberculosis infection, or at least contribute to its milder course.

Sometimes we observe a strange reaction in certain children. It happens that in a tuberculous environment one child does not become infected while others do, although they live under the same conditions. This fact is difficult to explain. But it is possible that in certain circumstances the thyocianate content of human saliva which restrains the growth of tubercle bacilli in a varying degree in different individuals may serve as an explanation of this fact (Zeyland).

The question of the hereditary predisposition to tuberculous infection and disease is still open, but we do not attribute a decisive influence to it. This point of view is proved by the French observations on the isolation of children from a tuberculous environment (*placement des tout petits*). These children were as healthy as the controls under the same conditions. The principal value in forbidding marriage between tuberculous persons consists, as far as the offspring are concerned, in avoiding the creation of a dangerous tuberculous environment. This point of view cannot be changed by experimental observations, which describe the possibility of obtaining strains of animals with greater hereditary resistance to tuberculosis than are generally found.

II. Prophylaxis of infection: It is concerned chiefly with infection with human bacilli. For instance in Poland in 72 cases examined (Piasecka-Zeyland) the bovine type of tuberculosis was found in only 5 children (ca 7 %) in spite of a very high percentage of infected cows; tubercle bacilli were found in 33—51 %

of samples of market milk. This is explained by the exclusive use of cooked milk in feeding children.

The prophylaxis of infection against human bacilli is now very well founded upon generally accepted and efficacious principles such as: the early recognition of every infectious case of tuberculosis, its earliest possible isolation and treatment in a hospital or sanatorium, the thorough examination of all contacts. It is necessary to remember, and generally it is not often enough considered, that young infected children who do not cough are also infectious, as they contain tubercle bacilli in their stomachs even in cases in which there are no visible pulmonary foci. I must also emphasize that the newborn infant may be infected by its tuberculous mother during the delivery, even if he is isolated immediately afterwards.

The efficacy of this procedure for prophylaxis is proved by the results obtained in many countries, especially in USA, where from 1900 to 1940 the mortality rate from tuberculosis decreased from 194.4 to 45.9 per 100 000 inhabitants. Of course the general improvement of hygienic conditions, the high degree of culture and of prosperity contributed to influence this decrease.

In less wealthy countries with smaller antituberculosis organizations the influence and the care of the health nurse from the antituberculosis center upon the tuberculous home, the early and appropriate instruction of the patient and of his family diminish the rate of infection of children to one-third (20 to 6 %) of the former rate.

The efficacy of all the above mentioned methods consists chiefly in the prevention of the infection of the small child and in postponing infection to a later time of life, when it does not produce tuberculous disease as often as in early childhood, when the organism is practically defenceless.

In Poland the situation is unfortunately quite different. Even before World War II. the mortality rate was very high. It amounted in 1931 to 200 and in 1938 to 175 per 100 000 inhabitants. It was practically as high as in the U. S. A. in 1900. In Poznan, for instance, the number of deaths from tuberculosis was as high in children from 0—5 years of life (chiefly in the first

three years of life) as in young adults (20—25). For every three deaths of girls between 10—15 years two were caused by tuberculosis. The situation grew worse after World War II. not so much as a consequence of the war itself as of the long occupation of our country by the enemy. The undernutrition which bordered on famine, the ruthless expulsion from their homes of a very high percentage of the inhabitants and the consequent very bad housing conditions, the concentration camps, the total destruction of our antituberculosis organizations, which we must reconstruct from the very beginnings — all this accounts for the enormous spread of tuberculosis in our country. It is now impossible to give quite reliable statistics, but according to the evaluation of the Ministry of Health 120 000 persons die yearly from tuberculosis and the number of tuberculosis cases amounts to 1 200 000 which is 5 % of the whole population. Krajewska J. and Kielanowski T. examined in Lublin radiographically 17 412 school children (total population 99 000) with the following results:

	Number examined	Without tbc.	Active tbc.	Suspect cases	Healed primary
Preliminary schools	379	253	82	19	25
Public schools	9 681	6 707	505	1 472	997
Middle & professional	5 666	4 438	219	384	625
High schools	1 686	1 413	105	121	47
Total	17 412	12 811	911	1 996	1 694

The percentage of active tuberculosis is 5.2, whereas in Germany, Holfelder found by the same methods for the years 1938—1941 only 2.5 %. Among children 3—7 years old the Polish authors found 21.6 % with active tuberculosis, and, excluding private schools, even 68 %! Generally in Poland 50 % of the children 7—8 years old have a positive tuberculin test, while Boulanger found in Paris only 24.5 % among children in the age group from 5—11 years (1944). The mastery of this situation and the creation of an appropriate prophylaxis requires time and financial means beyond the actual possibilities of our devastated

country. We cannot now prevent the spread of tuberculosis among our children by the previously mentioned classical methods. Unfortunately we often see fatal tuberculosis in a child indicating the existence of a tuberculous environment.

III. Inoculation with BCG: In these circumstances we must now and probably during the next years put a stress upon the vaccination of infants with BCG. We are basing our action upon the experience of other countries, as France, Sweden and Denmark, and upon our own experience before the war. The anti-tuberculosis campaign was then widely spread in Poland and especially in Poznan, where in connection with our clinic, the late prof. Zeyland, who was so tragically murdered in the insurrection of Warsaw, organized a vaccination center and made his classical researches on this method. His experimental research, together with his wife Piasecka-Zeyland E., and the observation of about 10 000 vaccinated infants convinced us that:

- (1) vaccination with BCG is absolutely harmless;
- (2) BCG given to the newborn by mouth penetrates into the organism and produces a positive tuberculin test;
- (3) this produces an immunity which is demonstrated by the lowering of the morbidity and mortality of children in a tuberculous environment:

	In the first year of life	
	morbidity	death from tbc.
among 147 inoculated children	16 (11 %)	3 (2 %)
among 62 controls	21 (33 %)	4 (6 %)

These results are very similar to those obtained by others (Heynsius, van den Berg, Park and his co-workers, Prokopowicz-Wierzbowska-Warsaw), but not as good as Wallgren's who attained such a low mortality as 0.3 per thousand. The reason for this was the impossibility of isolating all infants during the period of the development of immunity. However, this proves even better the efficacy of the inoculation.

In the evaluation of the efficacy of the inoculation we must consider: (1) The possibility of a lowering of the vitality of the bacilli CG under the influence of protracted cultivation on bile

medium, as it was shown by Zeyland and Piasecka-Zeyland. Better results were obtained by them after cultivating the bacilli on potatoes with glycerine and a passage on bile medium every two months. Before the war we abandoned subcutaneous inoculation, which produced strong local reactions (0.01 mg bacilli) in 37 % of 804 cases. In half of these, cold abscesses were observed and it was possible to cultivate the bacilli from them even after 6 months. The diminution of the dose to 0.005 mg gave only slight local reactions. Since the war we use only inoculation by mouth in newborns as we have now no vaccine for percutaneous use.

(2) Comparing the mortality and morbidity from tuberculosis among vaccinated children and controls we must consider the difference in the environment independently of the possibility of infection. As inoculation is not compulsory it is possible that the inoculated children come from more intelligent and careful families and that this and not the inoculation itself lowers the morbidity and mortality. This was proved by Levine and Sackett among 1 011 inoculated children and 1 073 controls.

Mortality rate from tuberculosis after non-compulsory inoculation:

Inoculated children.....	0.68 %
Controls.....	3.38 %

Mortality after inoculation of each second child:

Inoculated children.....	1.41 %
Controls.....	1.51 %

These authors conclude that inoculation with BCG in a tuberculous environment is less efficacious as a public health measure than the isolation of the source case from his home. And this is doubtless true. We mentioned above the efficacy of even the simple hygienic education of the tuberculous family. Of course still more efficacious is the isolation of the sick. But what is there to be done when there is no possibility of doing so? We must use inoculation with BCG even if our possibilities of isolation during the immunization are not as good as they should be. But we must emphasize that we consider the inoculation as only

one of the methods of prophylaxis against tuberculosis. All of them must be used, but in our very difficult conditions the inoculation is necessarily one of the chief methods of combating tuberculosis among children. And besides that, we must keep in mind that we have so many uncontrolled cases that the infection of a child, even of an infant, by a stranger is always possible.

Treatment.

I. The avoidance of superinfection is the first condition of an efficacious treatment of tuberculous children.

In adults the role of superinfection on the evolution of tuberculosis is not quite settled. In children the disadvantageous influence of it cannot be denied. Every day we see proofs of it. It is also proved by the observation of newborn infants infected by their mothers in the first day of life and then isolated from them. In spite of such early infection and severe primary tuberculosis a child can survive — one of these children observed in our clinic is now 15 years of age and has no clinical symptoms of tuberculosis.

II. The second condition is to secure to those children the best general hygienic conditions. In our country it is generally impossible to place such a child, particularly a small one, in an appropriate sanatorium. In spite of it we can in many cases assure to these children the fundamental conditions of treatment even at home, i. e., fresh air and good diet. We must free ourselves, particularly in our condition, from the suggestion that the treatment of active tuberculosis of childhood necessarily requires an appropriate climate, in the first place the foot-hill climate. The latter is too strong a stimulus for children with tuberculosis of the lungs. We must secure to these children the possibility of lying in the open air practically the whole day long. This can be achieved even in town if only the mother is convinced of the necessity of it in every season. This treatment must be continued till the improvement of the general condition and till the return of normal temperature and of a normal sedimentation rate. Without the complete fulfilment of this program we do not begin the treatment of tuberculous children. Gradually the child gets up

and begins his usual life, but always under the control of these three mentioned symptoms. We are often astonished how rapidly the sedimentation rate becomes normal after open air treatment — in these few days the local lesions cannot be changed. In some of these cases it is possible to find very slight symptoms indicating the existence of an additional infection, which is often overlooked. We think that this is important, because generally it is not taken into consideration how often tuberculous children are liable to different infections — it is the consequence of the anergic status during the tuberculous disease. We must consider this in the evaluation of our treatment. I mention this because lately Jaccottet M. and Nicod M. did not decide the question whether repeated infections of the respiratory system facilitate the tuberculous infection or whether they are the consequence of tuberculosis. I think that the latter opinion is correct. Besides the open air treatment excellent nutrition is decisive in achieving good results. It must be sufficient quantitatively and qualitatively. Considering the poor appetite usually at the beginning of treatment we must give frequent small meals, taking into account the individual liking of the child. This, however, cannot go so far as to lead to a one-sided diet, especially with a preponderance of carbohydrates. The diet must include the principal elements of nutrition; it must be rich in raw ingredients and vitamins. Skillful management, knowledge of the child's psychology and total devotion to this difficult task are indispensable for the achievement of good results. It can only be attained by the mother or a very good nurse.

III. Avoidance of every unnecessary stimulus is the third principle of treatment of tuberculous children. All powerful stimuli are invariably very harmful; they destroy the very unsteady equilibrium between the resistance of the body and the noxious influence of the infection. We must carefully avoid natural and artificial ultraviolet radiation (I omit here the treatment of bone tuberculosis). We must take this into account in open air treatment. And in our opinion every treatment with artificial ultraviolet radiation, if needed in other diseases, should be applied only after careful exclusion of tuberculous infection in small

children and of active tuberculosis in older children. The same restrictions must be applied towards saline baths and every kind of proteinotherapy, which is so often used by many physicians in every kind of acute fever in children after the first examination even before the exact diagnosis is established and also amongst others in acute stages of tuberculosis.

Acute infectious diseases must be reckoned among strong stimuli for tuberculous children. They are — particularly measles, whooping-cough and influenza — a menace to the health especially in large groups of small children. It is not easy to avoid them. The only prophylactic measure we possess is the convalescent serum against measles. However, we must emphasize that the noxious influence of these diseases on tuberculous children must be definitely settled. There is no doubt that measles, and in a lesser degree whooping-cough and influenza, cause a state of anergy for tuberculosis and other diseases, the result of which is an acute dissemination of tuberculosis, chiefly during the subsequent two months. However, the opinion is unfounded that the above mentioned diseases aggravate the local tuberculous changes in the lungs. Measles and whooping-cough very often produce chronic inflammatory processes in the lungs which were thought to be tuberculous in earlier times till the exact examination with tuberculin tests and Roentgen rays taught us that for the most part they are not specific. The opinion concerning the disadvantageous influence of influenza upon the local tuberculous lesion was based upon the mistaken diagnosis of an acute tuberculous process as an influenza.

IV. The pharmacological therapy of tuberculosis in children is of no great importance. It is only a symptomatic one. This also includes calcium therapy which is so widely used in all countries. We cannot say anything about treatment with streptomycin, but let us hope that it is the medicine we long for.

V. Collapse therapy and surgical treatment of pulmonary tuberculosis is very seldom used in children before the age of maturity when tuberculosis begins to resemble the adult form. Then of course these therapeutic measures must be applied even earlier than they are in adults.

CO-RELATOR.

Vaccination with BCG in the Prophylaxis of Tuberculosis.By **Alberto Chattás**, Cordoba, Argentina.

From the «Centro de Asistencia Médico-Social de la Tuberculosis» (Córdoba, R. A., Santa Rosa 974). Director Prof. G. SAYAGO.

Introduction.

Under the control of the Instituto de Tisiología of the University of Córdoba, directed by Prof. G. SAYAGO, we started in the year 1935, the vaccination with BCG in the City of Córdoba (R. A.).

The strain used in the preparation of the vaccine was brought in 1928 from the Pasteur Institute of Paris by Dr. A. ARENA, and was used for the first experiences (1). We were thus able to draw out some interesting conclusions and allowed us the systematic use of the BCG in the new born. The following table shows the number of vaccinated grouped by year, and the total amount which gives an idea of the work in our city.

TABLE No. 1.

Years	1935	1936	1937	1938	1939	1940	1941	1942	1943	Gral. total
Totals	26	50	770	827	1 396	2 878	3 627	2 829	3 040	15,916
Number of vaccinated in the city of Córdoba	(IV—1946)									22,254
Number of vaccinated in the city and Province	(IV—1946)									28,132

The number of vaccinated grew till it reached in 1941 almost the 50 % of the new born in the city, pertaining to the needy people, mostly assisted at the Public Maternity Hospitals, and the Asistencia Pública.

The vaccinated children were under the control of the BCG Division of the Instituto de Tisiología till the end of 1943, when the Staff had to leave the Institute. Now the vaccine is used only in the Instituto de Maternidad, that attends one third of the new born in the city, but it is no longer under our control. Several investigations made among the vaccinated, allowed us to

draw out conclusions which were published in several papers (2), (3), (4), (5), (6), (9), (13), (14), (15).

Epidemiological references.

In the Argentine the control of the human sources of infection, will not be reached for many years, on account of the scarce assistencial means, and the characters of the development of the disease, which is alike in all the countries with low density of population and a highly spread rural population. In consequence the need of protection against contagium in new born, school age children, and young adults, comes forth as the fundamental character of the antituberculosis campaign. The non possibility of control on the sources of infection, states in the 1st place, and as a fundamental means, the necessity of the vaccination.

The city of Córdoba, where our experiences of vaccination with BCG have taken place, is the capital of one of the most important provinces of the A. R., and had in 1944, 325 000 inhabitants. Its tuberculosis mortality in the same year reached to 187 per 100 000, amount which represents 13.6 % of the general mortality of the city (7). According to the references brought to the tuberculosis Congress of Havana by SAYAGO and GOMEZ CASCO (8) the tuberculosis infection revealed by the tuberculin tests, was:

TABLE No. 2.

City	{	10 to 15 years	49.2 %
		16 to 20 years	69.6 %
Province	{	10 to 15 years	42.8 %
		16 to 20 years	47.3 %

The incidence of asymptomatic tuberculosis in the case finding has shown: 0.7 % among high school students, and 7.08 % among the Dispensary Population with high exposure to disease (4.18 % of active first-infections and 2.90 % of active re-infections); among the school children who were tuberculin reactors, the active first-infections reached 7.23 % in rural schools of infected zones — and 4.1 % in town and suburban schools (7).

In the Argentine, the epidemiological characters of tuberculosis change according to the different regions. In general the

population density is low but the inhabitants are housed principally in the great cities. All the epidemiological investigations show differences between the tuberculosis infection in the city and in the country, but they all demonstrate that to a great amount the first-infection occurs most frequently between the age of 10 and 20 years, as it can be easily drawn out from the figures of tuberculosis infection in the city of Córdoba.

The tuberculosis prophylaxis should look upon the medical and social-economical problems created by the disease. From the medical point of view the assistencial problem of the patient with chronic tuberculosis is fundamental, and the antituberculosis campaign directed in that way is efficient only when it is able to control all the open cases, by means of sufficient hospitals or sanatorial-beds, or with the dispensary control over them. The discovery of asymptomatic tuberculosis through the survey of the population is an important complement in every efficient antituberculosis campaign, because it offers the possibility of control over the disease in its early stages, when the cure possibilities are then great. Finally, the prevention of the disease among non infected since birth, either by separating the source of infection, or protecting them against the danger, by means of the BCG vaccination.

The isolation of the known cases in Hospitals or Sanatoriums is not proportional to the annual deaths. On the other hand the allergical information and X-Ray control of the population to determine the degree of expansion of the infection, and to discover the asymptomatic cases, whose danger of contagium is well known, has not reached in our country the convenient intensity. We are far from reaching a proportional and convenient assistencial program for the chronic cases.

Our knowledge permits us to state that individuals who have passed through a mild first-infection, are in better conditions against tuberculosis re-infection.

The individual that by means of vaccination is able to acquire such conditions as are given by a mild first-infection, is also able to resist better a re-infection and free from the danger of virulent first-infection.

Brief technical report.

In our practice we have mostly vaccinated the new born, using several techniques, that allowed us to study the tolerance to the vaccine, the reactions it produced and the response to the tuberculin test (9). We chose among the new born those who weighed more than 2 500 g. not because we believed that the BCG could do any harm to a premature baby, but because the organic conditions of the last can suffer disorders which we did not wish to be attributed to the BCG.

The first-vaccinations were done by the oral method in three doses of 0.01 g. every other day; later on, three doses of 0.02 g. were used, and finally in a limited experience made on elder children — from 5 months to 14 years of age — a unique dose of 0.20 g. was administered. The total number of vaccinated by the oral method was 453 children.

We vaccinated new born by subcutaneous method using mostly a dose of 0.04 mg. The total amount vaccinated was 436.

In the intracutaneous method we used 0.02 mg. till we reached the dose of 0.30 mg. but the one most frequently used was of 0.15 mg. The intradermic method was used in almost all the vaccinated children. By the end of April, 1946, the total vaccinated by this method reached the number of 21 150 in the city and of 27 028 in town and province.

We also tried the multipuncture vaccination as recommended by Rosenthal, in 46 children and the method of scarification used by Negré and Weill-Hallé in 169.

Owing to practical reasons we have preferred to do the intracutaneous vaccination in one dose; in this way we believed to obtain uniformity and to increase the number of vaccinated employing only a few nurses, and to avoid the possibility of incomplete absorption in the oral method as it happens when the baby vomits it. We do not wish to express, by any means, that the other methods are less efficient, but it is useful to remember that the oral, intracutaneous or subcutaneous vaccination must be done in the best possible conditions, so as not to give a false security on the wrongly vaccinated child, especially when the results can not be controlled.

The experience made on several groups of children, in a comparative way, and for a control purpose, allowed us to draw out some interesting conclusions and to use the vaccine in the routine work. To vaccinate and to isolate the child till it becomes a tuberculin reactor, represents the orthodox conduct, and thus we acted when knew of a familiar source of infection; but owing to practical reasons, and to other author's experiences we did not do so in a great part of the vaccinated. Besides the groups of children in which the vaccination was controlled, the most important number, was vaccinated without knowledge of the household conditions. It can be objected that to vaccinate a child without isolation, leaves it in bad conditions against contagium, at least till it becomes reactor. But experience shows, that even under those conditions the vaccinated child would not be in a worse situation than a non vaccinated in the same household exposure (ASSIS and CARVALHO and CHAUSSINAND) (10), (11).

General, local and allergic reactions in the vaccinated.

A group of children was controlled to study the characteristics of the vaccinal nodule and of the apparition of the allergy in them.

The oral vaccination did not produce in the new born or in the elder children disorders of any kind; it was perfectly tolerated, without diarrhea or loss of weight, which could be beamed to BCG.

With the subcutaneous vaccination we saw, as other authors did, a greater tendency to form abscesses; only in two instances we had to puncture, evacuating 2 cc. from one, and 4 cc. from the other of fluent pus; the culture of which did not show any germs. Generally abscesses cured spontaneously.

With the multipuncture vaccination and also with the scarification method we noticed little indurative, sometimes suppurative reactions which cured leaving punctiform or lineal scars.

In the intracutaneous injection the frequency and importance of the vaccinal nodule were different depending on the administered dose.

In a group of 256 intracutaneous vaccinated with 0.30 mg., that was lately under our control, we observed:

205 with nodules of several sizes (80.07 %)

15 without nodules (5.85 %)

11 with closed abscesses (4.29 %)

15 with open abscesses (5.85 %).

The nodule of the first vaccination has in its evolution differences to the one produced by a revaccination. The first-vaccination does not produce during the first two weeks anything abnormal in the place where the BCG was injected; only after 14 days an infiltration is noticeable which grows up to 4 to 6 mm reaching its maximum between the 21st and the 28th day, decreasing and disappearing between the 60th and 160th day. A light induration or an achromic spot is left temporarily there, as a remains of the small nodular abscess.

In the place where BCG is injected with re-vaccination purpose a nodular reaction tuberculin-type is noticeable 24 to 72 hours later, whose infiltration corresponds to a 1 or 2 plus. This infiltrative reaction grows smaller till the end of the first week, without disappearing; it grows bigger then between 12 and 30 days till the nodule, reaches a greater size than it is observed in the first-vaccination (1.5 to 2 cm diameter). Then it begins to disappear until it heals within 3 to 4 months (9), (17).

We put the intracutaneous injection of the vaccine in the right scapular region in some groups, and in others, in the flexor surface of the forearm.

The regional lymphglands reactions, were not noticed with the frequency that other workers did we only observed the swelling of regional glands mostly in children with eczema, and in no case supurations, the regional gland reaction disappear when the nodule heals. The greater frequency of supurative regional nodes observed by other authors, who vaccinate in the thigh, can be due in the baby, to the secondary infection to which it is exposed, due to the contact with diapers. We must also consider, in these cases, a greater virulence of the strain of BCG used in the preparation of the vaccine.

By studying the *allergic conditions*, we were able to see that BCG can produce a positive tuberculin reaction, easy to control under given conditions.

The allergic control was made on a selected group of vaccinated, using 0.1 cc of a dilution of 1 per cent OT (1 mg) by intracutaneous injection; if there was no reaction we used then the 1 in 10 dilution (10 mg); we only use the dilution 1 per 1 000 when we suspect or know an infected surrounding. We read the reaction of tuberculin test as recommended by the National Tuberculosis Association.

Our statistics show that the frequency of positive reactors when the intracutaneous vaccination is used, reaches at the 6th month a percentage between 80 and 100 %.

The characteristic of the vaccinal allergy, according to the majority of the observers, is: that it appears in a progressive form; it is of low or medium intensity and it needs sometime, in order to show up a test with 10 mg of tuberculin intracutaneous; it is regressive until complete disappearance, passing through a stage in which it becomes *inapparent, latent, or infratuberculinic*.

The allergic study of a group of children vaccinated sometime ago, showed that in several cases they became non-reactors with 10 mg of OT injected intracutaneously. The existence of a residual allergy was demonstrated when to these children according to the advice of ASSIS, 0.15 mg of dead BCG were intracutaneously injected, they became positive reactors after eight days (12) undoubtedly this state of infratuberculinic or residual allergy helps to the early evidence of the nodule and gives it, special characters in the re-vaccination; this is known as the WILLIS-SAYE's phenomenon.

An intense positive tuberculinic test, of a vaccinated, means sometimes a virulent infection, specially when it happens in the stage when the allergy should decline.

The knowledge of the existence of vaccinal allergy and its characteristics, is in Pediatrics of the utmost importance, owing to the fact, that the vaccination with BCG is wider spread; and creates to the physician who is not aware of its existence, the problem of its interpretation (13). The allergy by infection can be

mostly classified as hyperergic and can be revealed by smaller doses of tuberculin than is necessary to investigate the BCG allergy, and does not decline but in a reduced percentage.

Observing the results of the tuberculin test in vaccinated and infected non-vaccinated groups of children, we saw in the first one that the allergy diminished in time, in intensity and frequency, while in the second group, it presents itself oftener in the course of time and the graph shows a progressive increase of same (3). It is very important, besides, to know the householding condition where the vaccination is performed, with the purpose of knowing when the allergic response is due to the infection or to the vaccination.

Our experience leads us to the conclusion that the positive tuberculin test in oral vaccinated, appear much more slowly (between the 2nd and 3rd month) but generally persists for more than 2 years after the vaccination. In this group of vaccinated we saw a 50 % of reactors.

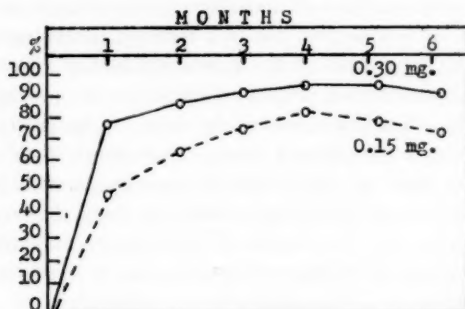
The appearance of allergy, according to our experience presents itself much earlier in subcutaneous than in the oral vaccination (in the 3rd or 4th week) reaching its maximum frequency (58.8 %) at the 6th. month (9).

In the year 1938 during the study of the response of the tuberculin test in 245 intracutaneously vaccinated with 0.02 mg at the Instituto de Maternidad we obtained 60.4 % of positive reactors; and later when the dose was increased to 0.15 mg the number of positive reactors at the end of the first month, reached 98.3 % (babies born in the San Roque Hospital Maternity) (14).

Up-to 1943 we used the vaccine prepared in the Instituto de Tisiología of Córdoba, but owing to having left the Institute, we started new observations in a group of babies vaccinated with the intracutaneous method. Using a vaccine prepared in Buenos Aires we noticed that with a dose of 0.15 mg the positive reactor were 84 % and with 0.30 mg they reached 95 % at the end of the 4th month (Graph No. 1) (15). Thus we come to the conclusion that to a higher dose of BCG corresponds a higher percentage of positive reactors.

In the vaccinated by the scarification method we obtained

GRAPH NO. 1.



from 75 to 100 % positive reactors, depending whether we made 3 or 6 scarifications or putting on same BCG in the dilution of 0.01 or 0.03 g per cc. Likewise with the multipuncture method the frequency of positive reactors varied between 70 to 100 % depending if we made 10 or 30 punctures or used less or more concentrated BCG.

We have observed that in the multipuncture or scarification method the tuberculin test became positive very early; between the 7th and 15th day.

In short, the frequency of reactors with the tuberculin test depends on the doses of BCG and the method of vaccination employed. The age of the culture used in the preparation of the vaccine has been, with reason, pointed out by other authors as a definite factor in the frequency of production and early appearance of the allergy; the 15 days culture that were employed in the Córdoba vaccine appear to be the most favorable in this sense. It is wise to call the attention to the existing differences depending on the culture mediums and the technique employed in the preparation of the vaccine.

These facts lead us to the conclusion that the vaccination must be performed on the base of a certain technique in the preparation of the vaccine, administering it and of uniform doses.

The difference between the allergy of vaccinated and non-vaccinated children, of the same age and of the same household contact

is shown in the following table corresponding to a comparative study of 224 children (14).

TABLE No. 3. Allergic study of vaccinated and non-vaccinated children between the ages of 2—10 years.

Vaccinated (112 cases)						Non-Vaccinated (112 cases)					
Anergic		Allergic				Anergic		Allergic			
Exposed	Not ex-posed to	+	++	+++	++++	Exposed	Not ex-posed to	+	++	+++	++++
3	14	43	27	14	11	19	20	17	11	26	19
17 cases (15.2 %)		Weak 70 cases (73.7 %)		Intense 25 cases (26.3 %)		39 cases (34.9 %)		Weak 28 cases (38.5 %)		Intense 45 cases (61.4 %)	
		95 cases (84.8 %)						73 cases (65.1 %)			

From the preceding table we gather that the positive reactors among the vaccinated reached to 84.8 %; it means a very high proportion considering that it was observed at least two years after vaccination, which was performed a few days after birth. Among the non-vaccinated they reached to 65.1 %. Most of the vaccinated were weak reactors (73.7 % with one or two plus); on the non-vaccinated, a weak response reached to 38.5 % and the intense response to 61.4 %.

X-Ray control in vaccinated.

Roentgen pictures in small films (35 mm) according to Abreu's method, were taken to all the vaccinated children; which were under our supervision and belonged to infected households, and showed a strong response with the tuberculin test. If this reduced film showed suspicious shadows, a panoramic chest film was taken.

The study of the changes in the X-Ray pictures taken on vaccinated and non-vaccinated, exposed and not exposed to infected sources was an interesting experience.

The results of the X-Ray picture control over 112 vaccinated,

and 112 non vaccinated children, are resumed in Table No. 4, which belongs to a report made together with SAYAGO and DEGOY, before the 6th Panamerican Tuberculosis Congress, held in Havana, 1945 (14).

TABLE No. 4. X-Ray picture changes, found in children between 2 to 10 years of age, belonging to similar contact households, vaccinated at birth and non-vaccinated.

Vaccinated (112 cases)				Non-vaccinated (112 cases)			
Exposed 33 cases		Non-exposed 79 cases		Exposed 70 cases		Non-exposed 42 cases	
With lesions	Without lesions	With lesions	Without lesions	With lesions	Without lesions	With lesions	Without lesions
19	14	15	64	52	18	20	22
57.5 %	42.4 %	18.9 %	81.0 %	74.3 %	25.7 %	47.6 %	52.3 %

Resuming the results of table No. 4, in an objective way, we can say that: from the roentgenological point of view the vaccinated showed normal pictures in 78 cases (69.7 %) and lesions in 34 cases (30.3 %) while in the non-vaccinated only 40 showed normal pictures (35.8 %) and 72 lesions (64.2 %); we can see then, that among non-vaccinated the number of lesions showed in the X-Ray pictures, was twice the number compared with the other group.

The X-Ray film changes found in the group of vaccinated exposed reached 57.5 %, being less significative in the radiological aspect, while in a non-vaccinated group also exposed, showed not only more frequency (74.3 %) but also more significative. The following table No. 5 will allow us to understand better what we have said.

These results show that whether in a known or unknown contact, the vaccinated child reacts in better conditions than the non-vaccinated.

In that same report presented with SAYAGO and DEGOY (14), we inform about the tuberculin test and the X-Ray changes in 51 children, 7 years after the vaccination with BCG. This obser-

TABLE NO. 5.

X-Ray film changes	Vaccinated (34 cases)	Non-vaccinated (72 cases)
Uni or bilateral swollen hilum nodes..	16 cases (47.0 %)	19 cases (26.6 %)
First complex	9 cases (26.4 %)	33 cases (45.8 %)
Soft nodes in hilum	7 cases (20.5 %)	8 cases (11.1 %)
Calcificated nodes in hilum	1 case (2.9 %)	11 cases (15.2 %)
Soft nodes in parenchyma	1 case (2.9 %)	1 case (1.3 %)
Totals	34 cases	72 cases

vation was rendered possible because the children were in an orphan asylum where one of us (DEGOY) worked. A survey was made on all the adults who worked in the institution, so the existence of a householding contact was dismissed and the occasional infection remained as the most important. Table No. 6 which resumes the results of the X-Ray films, show lesions only in 7.8 %, that is to say in one fourth of the children observed in the Dispensary, mentioned above (Table No. 4).

TABLE NO. 6.

Total of vaccinated 51	
X-Ray film	{ Normals 47 = 92.2 % { Pathological 4 = 7.8 % ¹
Tuberculin reaction in the vaccinated	Tuberculin reaction in pathological cases
Last test 7 years after vaccination Neg. 11 cases = 21.5 % + 9 cases = 17.6 % ++ 22 cases = 43.1 % +++ 9 cases = 17.6 %	Neg. 1 case + 1 case ++ 2 cases

¹ They are { 3 swollen hilum lymph nodes
 { 1 first-complex (residue).

We can see in this group that seven years after BCG 40 children were still positive reactors; only 9 showed three plus (17.6 %) and only 11 (21.5 %) became non-reactors.

Investigation of the tubercle bacilli in vaccinated and non-vaccinated.

The investigation of the tubercle bacilli in stomach content was done in 20 vaccinated and 20 non-vaccinated children, in which we were able to study the results of the tuberculin test, the X-Ray film changes and the contact householding.

The inoculation of the guinea pig, gave positive result in 2 vaccinated (10 %) and negative response in 18. In the non-vaccinated 9 (45 %) were positive and 11 negative (9).

These figures show that the lesions in the vaccinated group are less significative.

Tuberculosis mortality in vaccinated.

The conditions under which we have done our work, do not allow us to study the tuberculosis mortality statistically in a large scale. Still as we have already said (9), we were able to compare 2 groups of 20 children each, vaccinated and non-vaccinated, belonging to similar contact surroundings. In these children the tuberculosis mortality was 5 % in the vaccinated and 10 % in the non-vaccinated.

In another paper (14) we studied the general mortality in several groups of vaccinated in the city of Córdoba (1941—42) which reached to 3.33 % in the first year of life; while in the whole city at the same time and age of life, it was 12.4 %.

We were able to check three vaccinated children who died of generalized tuberculosis. Two of them, were infected with virulent tuberculosis in the first days after the vaccination, and the third one at the age of 18 months during a measles. In the three cases the contagious contact took place when the resistance against the infection produced by BCG is supposed not to be present.

Revaccination.

Since the allergy given by the BCG is not permanent, and disappears in the course of time, the need of revaccination is quite clear.

In spite of the absence of positive tuberculin test we could observe, in the cases in which we practiced a re-vaccination,

(VARGAS SIVILA) (16) that the response was different when they received a new dose of BCG, comparing it with the first vaccination: the re-vaccinated become earlier positive reactors, and the vaccinal nodule as we have seen grows in a different way (17).

Summary.

1°) Our experiences confirm the conclusions of most of the papers published up to the present, about the *inocuity of BCG in the new born, and in the older non-infected.*

2°) The statistics of Córdoba (R. A.) were drawn out of a total of 22 254 vaccinated in the city, making a total of 28 132 including the vaccinated in the rest of the province.

3°) The vaccination was preferently done on new born, and in a smaller number among older children.

4°) The following methods were used: oral, subcutaneous, multipuncture, scarification and intracutaneous. Most of the children were vaccinated with the last method in a dosis of 0.15 mg.

5°) The tuberculin test was done generally with 1 mg of OT, injected intracutaneously. From this, we gather that the incidence of reactors reaches 95 % of the intracutaneous vaccinated.

6°) *The efficiency of the vaccination*, is deduced from our comparative studies between vaccinated and non-vaccinated, belonging to similar contact household.

a) *The tuberculin test* showed milder response (one or two plus) in the vaccinated than in the infected non-vaccinated (hyperergic).

b) *The changes in the X-Ray films*, studied in 2 groups of 112 children each, both between the ages of 2 and 10 years, one group vaccinated at birth, and the other non-vaccinated showed: Among exposed vaccinated, 57.5 % of lesions, and in exposed non-vaccinated 74.3 %. Among non exposed, the incidence of lesions, was 18.9 % in the vaccinated, and 47.6 % in the non-vaccinated. This favorable difference in vaccinated children, is not only numerical but it is also less significative in the anatomo-radiological changes shown by the film.

7°) The investigation of tubercle bacilli in the stomach contents, made in 20 vaccinated and 20 non-vaccinated children, both with household contact and with changes in the X-Ray films, showed positive result in 10 % of the vaccinated, and 45 % of non-vaccinated.

8°) In the Latin American Countries, where the first-infection problem not only deals with the child but also with the young adult in a high proportion (50 %), there is a need of vaccination in a large scale, while the assistance resources are not enough to control all the open cases.

9°) We therefore come to the conclusion that a Committee or Laboratory is needed which would centralize the investigation, in order to uniform the preparation of the vaccine and the method of its use, with the purpose of obtaining results which could be compared.

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CO-RELATOR.

Chancres tuberculeux extra-pulmonaires, notamment chancres Gingivo-Jugaux.

Par Robert Debré et Stéphane Thieffry, Paris.

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L'infection tuberculeuse de l'enfant peut débiter par une lésion cutanée ou muqueuse. S'il est hors de doute que dans l'es-

pièce humaine la lésion initiale siège aux poumons dans la très grande majorité des cas, il est aussi fermement acquis que le chancre et son satellite ganglionnaire peuvent se manifester ailleurs, devenant ainsi patent aux yeux du clinicien et non plus à ceux du radiologiste.

La fréquence comparée des manifestations anatomiques initiales pulmonaire et extra-pulmonaires ressort clairement de la statistique déjà ancienne (1909)¹ d'Albrecht rapportée par Ghon où, en regard de 1 046 localisations pulmonaires, on ne peut reconnaître plus de 14 chancres extrapulmonaires, chiffre d'une faiblesse insigne encore amenuisé par des interprétations nécessairement douteuses dans quelques observations. C'est une proportion du même ordre qui fut signalée dans des travaux ultérieurs, en particulier la statistique de Ribadeau-Dumas, Robert Debré et Rolland.²

La localisation initiale extrapulmonaire de la tuberculose mérite cependant mieux qu'une mention dans une statistique. Une expérience personnelle nous a permis d'en étudier un certain nombre de cas. Nous limiterons cet exposé à quelques remarques sur la tuberculose initiale de la peau, déjà signalée à maintes reprises et bien étudiée dans ses grandes lignes, et surtout à une étude plus complète de la localisation initiale gingivo-jugale que nous croyons mal connue et en tout cas, ne semble pas avoir suffisamment retenu l'attention des médecins d'enfants et des dentistes.

A l'occasion des localisations tuberculeuses initiales cutanées ou muqueuses, il nous paraît essentiel de distinguer formellement le problème doctrinal et le problème clinique. Une question est de savoir si on peut réaliser la tuberculisation d'un sujet donné par la voie transcutanée ou par la voie muqueuse, une autre est de reconnaître la lésion locale provoquée par la pénétration en

¹ GHON et WINTERITZ, La question du début de la tuberculose, pulmonaire et extrapulmonaire chez le nourrisson et l'enfant. *Zeits. für Tuberkulose*. Mai 1924, p. 147.

² RIBADEAU-DUMAS, ROBERT DEBRÉ et ROLLAND, La lésion initiale de la tuberculose pulmonaire. (*Soc. Méd. des Hop. de Paris*, 1^{er} Mai 1914, p. 789.)

un point déterminé de la peau ou des muqueuses, d'en distinguer les caractéristiques cliniques, d'en suivre l'évolution. Au problème doctrinal, qui sort des limites de cette étude, se rattache, on le sait, toute une partie de l'oeuvre de Calmette. L'expérience a montré l'indifférence habituelle des muqueuses vis-à-vis du bacille tuberculeux, qui peut les traverser sans laisser la moindre trace de son passage. On a vu aussi que la peau en apparence intacte est loin d'être un obstacle infranchissable pour le bacille tuberculeux. L'absence de lésion cutanée ou muqueuse n'est pas, en principe, un argument suffisant pour nier l'existence d'un mode extrapulmonaire de contamination. Par contre, grâce à de multiples expériences, on peut se convaincre de l'importance d'un traumatisme préalable pour fixer *in situ* le bacille tuberculeux et le retenir en quelque sorte à l'endroit où il a été déposé. C'est ainsi qu'en procédant au laboratoire à une altération préalable de la peau par des procédés mécaniques tels que la friction, l'épilation ou mieux encore une scarification légère, on fixe l'agent pathogène et on produit alors une lésion locale visible, palpable, durable.

Il est inutile d'insister sur l'intérêt pratique de cette notion, en ce qui concerne le mode d'administration du vaccin B. C. G. A la méthode initiale de Calmette basée sur la possibilité de traversée de la muqueuse intestinale par le bacille, s'est substituée la méthode d'introduction directe du vaccin dans le derme (Wallgren), puis dans l'épiderme (Rosenthal) à la faveur de scarifications superficielles réalisant le traumatisme juste nécessaire pour fixer à la peau le bacille vivant et atténué. A ce titre, on peut considérer la réaction locale observée au cours de la vaccination comme un exemple de lésion tuberculeuse initiale mineure et dégradée, et même comme la mieux connue des localisations initiales puisque Nègre et Bretey ont pu en suivre presque heure par heure l'évolution anatomique.

La tuberculose primaire de la peau, telle qu'on l'observe au hasard de la clinique, est un accident relativement rare. Tout pédiatre en connaît cependant plusieurs exemples. A plusieurs reprises, depuis l'observation princeps d'Albrecht elle a été l'oc-

casion d'une étude d'ensemble. Nous-mêmes en avons rapporté plusieurs observations¹ et depuis l'attention a été attirée sur ce point particulier.²

On peut, en principe absolu, affirmer l'origine traumatique de l'accident. Les exemples les plus typiques ne manquent pas où se joignent la notion d'un contact précis avec un sujet tuberculeux dont la salive ou l'expectoration a souillé la peau préalablement traumatisée. Par contre, chez l'enfant déjà grand, il y a lieu d'invoquer le contact avec des poussières bacillifères de la rue ou des planchers. C'est le cas par exemple des tuberculoses cutanées du genou par plaie accidentelle. On conçoit d'ailleurs que suivant l'âge de l'enfant, suivant les circonstances du traumatisme, suivant les hasards de l'accident, les localisations les plus diversés ont été notées: mains, tronc, cou, et surtout face et membres inférieurs.

La lésion cutanée développée à la porte d'entrée du bacille et son adénopathie satellite constituent par leur étroite et constante association un «complexe cutanéoganglionnaire» qui doit mettre sur la voie du diagnostic.

La lésion cutanée est presque toujours de taille si réduite qu'elle est négligée par les parents, beaucoup plus inquiets d'une adénopathie volumineuse que d'une plaie minime. La lésion a été décrite à des stades très divers de son évolution. On peut en proposer la description schématique suivante: elle est souvent recouverte d'une croûte brûnâtre, qui cache une ulcération peu profonde à fond rouge, légèrement suintant, mais finement irrégulier et grenu. Les bords ne sont pas décollés, mais surélevés en talus circonscrivant l'ulcération centrale, d'une teinte rougeâtre ou rosée ou violacée. Le chancre cutané peut être légèrement douloureux. Il est généralement souple et laisse sourdre à la pression un peu de sérosité ou de pus.

¹ ROBERT DEBRÉ, J. MARIE et A. MALINSKY, Sur le chancre tuberculeux initial de la peau chez l'enfant. *Revue Française de Pédiatrie*, T. XIV, N° 1, 1938.

² Dans l'impossibilité de reprendre toute la bibliographie de la question, nous nous contenterons de rappeler: Magalhaes, Le complexe primaire tuberculeux de la peau dans l'enfance. *La Prensa Medica Argentina*, 1, 8, 15 Juillet 1936, étude de 86 observations.

L'adénopathie apparaît ou augmente de volume quelques jours après la formation de l'ulcération. De volume important et même considérable, elle a une tendance à se ramollir et à se fistuler présentant alors l'aspect typique des adénites tuberculeuses.

Cette lésion primaire locale a, comme toutes les lésions primaires, une tendance nette à guérir spontanément. Cette guérison locale demande plusieurs mois pour l'ulcération, un à deux ans pour l'adénopathie.

Ainsi se poursuit dans le temps la disproportion entre la lésion cutanée d'inoculation et son adénopathie similaire. La lésion cutanée avant de s'effacer peut prendre un aspect verruqueux ou lupiforme, fait à connaître et à distinguer des greffes secondaires de tuberculose verruqueuse ou de lupus qui peuvent se développer sur la cicatrice d'une biopsie.

Nous reportons plus loin l'étude du diagnostic et du pronostic de la tuberculose primaire cutanée.

Parmi les tuberculoses primaires des muqueuses, celles de la gencive semblent avoir une importance sur laquelle on n'a pas suffisamment insisté jusqu'ici. Autant la littérature médicale est riche de tuberculoses primaires de la peau, autant sont rares les descriptions de la tuberculose gingivojugale primaire. Quand en 1941 nous identifiâmes personnellement nos premiers cas, nous ne pûmes trouver que deux observations^{1 2}. En réalité, la première identification de cette entité morbide est l'oeuvre d'Akerberg.³ Depuis qu'à l'occasion de nos publications personnelles⁴, l'attention des pédiâtres et des stomatologistes a été attirée sur ces faits, les observations se sont multipliées, surtout dans le milieu des spécialistes. Il ne se passe pas d'année où nous n'ayons l'occasion d'observer de nouveaux cas. Nous possédons actuel-

¹ A. VALLETTE et B. ROSENKRANZ, Chancere tuberculeux gingival. *Bul. Soc. Pédiatrie*. Paris, 4 Juillet 1936.

² J. CATHALA et LEMERLE. Primo-infection à porte d'entrée gingivale *Bul. Soc. Pédiatrie*. 21 Janv. 1941.

³ AKERBERG, Deux cas d'accidents primitifs tuberculeux de la peau et de la gencive. *Acta dermatovenereologia*, T. XIV, N° 1. Juin 1933.

⁴ S. THIEFFRY et R. MANDE, Chancres d'inoculation tuberculeuse initiale de siège gingival (*Soc. Péd. Paris*, 20 Janv. 1942.)

lement neuf observations de tuberculose initiale gingivojugale, ce qui fait penser que l'affection une fois connue apparaîtra d'une fréquence assez grande et peut-être supérieure à celle des chancres tuberculeux cutanés.

Deux modes de début peuvent être opposés, si différents par leur acuité ou leur latence, leur allure inflammatoire ou froide, que c'est tantôt le stomatologiste et tantôt le médecin qui est interrogé le premier.

Parfois l'accident tuberculeux primitif simule une maladie locale aiguë de cause dentaire ou paradentaire. Il y a de la fièvre et des douleurs et l'on constate, au point qui sera ultérieurement le siège d'une ulcération, un véritable abcès de la gencive, qu'on attribue à un accident dentaire, à une carie de voisinage, à une périostite ou même à une ostéite.

Dans d'autres cas, l'accident muqueux se développe en silence, sans douleur. La maladie débute apparemment par une adénopathie sous-maxillaire. C'est alors l'examen systématique de la bouche qui fait découvrir l'ulcération.

Quoiqu'il en soit, deux éléments entrent en ligne de compte: une ulcération muqueuse et une adénopathie sous-maxillaire localisée. L'ulcération semble précéder l'adénopathie mais on ne peut affirmer qu'il en soit toujours ainsi.

L'ulcération a des caractères spéciaux. Elle tranche peu sur le reste de la muqueuse, siège presque toujours (sauf une fois) à la mâchoire inférieure, soit au collet d'une dent, soit presque toujours — et c'est là un aspect presque pathognomonique — dans le sillon gingivojugal, repliée sur elle-même, en feuillet de livre. Elle apparaît régulière, ovale, son grand axe orienté suivant le sillon gingivojugal, long de un à deux centimètres. Le fond est propre, ne suinte pas, mais peut être parsemé d'un semis de petits points blanchâtres ou jaunâtres. Ces bords sont légèrement surélevés. Parfois cette ulcération semble reposer sur une base indurée, il existe alors un véritable abcès froid sous-jacent qui peut s'ouvrir, évacuer son contenu et laisser une fistule à bords décollés, menant directement sur le périoste et pouvant même donner issue à des séquestres osseux lamellaires.

L'adénopathie a tous les caractères des adénites tubercu-

leuses. Elle est de volume important, résulte de l'intumescence d'un ou plusieurs ganglions qui sont toujours exactement situés dans le territoire satellite de l'ulcération. Au cours de l'évolution, cette adénite a tendance à se ramollir et à se fistuliser.

Dans les cas habituels, la lésion initiale tuberculeuse gingivale guérit, en évoluant, comme une affection locale, mais très lentement curable. L'ulcération de la muqueuse peut persister pendant des mois ou même plus d'un d'une année. L'adénopathie se fistulise généralement. Elle est encore nette, trois ans après le début dans une de nos observations.

Les lésions initiales de la peau et des muqueuses donnent au médecin l'occasion de vérifier une fois de plus l'unicité des processus pathologiques déclenchés dans l'organisme humain à l'occasion de sa rencontre avec un bacille tuberculeux pathogène. Que ce soit au poumon, à la peau, ou à la muqueuse que pénètre pour la première fois le bacille de Koch, il détermine là où il arrive une lésion locale et une adénopathie à contenu caséux dans le territoire afférent du chancre d'inoculation. Cette association obligatoire d'une lésion locale et d'une adénopathie satellite est une des premières conditions à respecter pour envisager sans risque d'erreur le diagnostic d'une telle lésion. C'est ainsi qu'il faut envisager d'un esprit critique les observations de tuberculoses cutanées ou muqueuses verruqueuses ou lupiques qui ne possèdent pas l'attribut ganglionnaire, et avec des réserves encore plus grandes les adénites cervicales tuberculeuses, qui ne correspondent pas à une ulcération buccale.

La difficulté n'est pas de reconnaître la nature tuberculeuse, mais plutôt d'affirmer qu'il s'agit de tuberculose initiale.

La seule preuve formelle de la nature primaire d'une tuberculose cutanée ou muqueuse est apportée par la notion de l'absence de toute sensibilité tuberculinique avant l'éclosion de la lésion, condition qui est d'ailleurs réalisée dans un grand nombre d'observations. A cet égard, des observations comme celles de L. Bernard et ses collaborateurs¹ occupent une place privilégiée

¹ L. BERNARD, M. LELONG, M. LAMY et P. GAUTHIER-VILLARS, La primo-infection tuberculeuse par inoculation cutanée, *Ann. de Médecine* 1931. T. XXX, p. 401.

en démontrant la précession possible du chancre cutané sur la première cuti-réaction positive, l'écart entre la constatation de la lésion et l'installation de l'allergie pouvant atteindre trois semaines.

S'il est impossible, faute d'explorations antérieures de l'allergie, d'affirmer la coïncidence, il n'en reste pas moins une série d'arguments cliniques, évolutifs, bactériologiques et anatomiques, qui constituent un faisceau de preuves suffisantes pour affirmer qu'il s'agit bien de tuberculose initiale.

On ne saurait assez insister sur l'importance des manifestations initiales qu'avec Marcel Lelong¹ nous plaçons dans la phase secondaire précoce: la kerato-conjonctivite phlycténulaire et surtout l'érythème noueux dont l'apparition est relevée avec une assez grande fréquence dans la tuberculose primaire cutanée (6 fois sur 90 cas) et deux fois en même temps que le chancre gingival (Vallette — Obs. personnelle). Pour avoir moins de force évocatrice, la constatation d'une onde fébrile prolongée et sans rapport avec l'infection locale est un symptôme qui ne peut être négligé.

Des arguments évolutifs fort importants viennent éclairer la nature exacte des lésions initiales cutanées ou muqueuses. Il est constant que le cliché radiographique ne révèle jamais la moindre anomalie, aucune des modifications dans la primo-infection gangliopulmonaire commune et plus tard aucune calcification.

Le pronostic local des tuberculoses initiales de la peau ou des muqueuses est celui que nous avons vu. Le pronostic vital n'est pas, semble-t-il, beaucoup plus sévère que celui des tuberculoses à localisation pulmonaire initiale. C'est ainsi que Magalhaes² sur 86 cas de chancres cutanés compte 13 décès, chiffre qui peut paraître énorme, mais qui s'explique mieux si l'on se rappelle qu'ils concernent uniquement des nourrissons (13 décès sur 31 nourrissons). Nous-mêmes comptons deux décès sur un groupe de neuf chancres gingivaux. Quoi qu'il en soit, quand la mort

¹ ROBERT DEBRÉ et M. LELONG, *Traité de médecine des enfants*, T. II. Paris 1934.

² MAGALHAES, *loco citato*.

survient, elle est le résultat d'une dissémination ou d'une méningite tuberculeuse. Nous notons personnellement que ces accidents sont précoces, souvent trois mois après le début de la maladie, c'est-à-dire à un stade où on peut les redouter au cours de toute tuberculose d'invasion. Nous pouvons ajouter que l'examen anatomique des viscères révèle alors l'absence des lésions communes d'adénopathie trachéobronchique, et l'existence de tubercules disséminés du foie, de la rate avec formations folliculaires.

Ceci nous amène à envisager ce qu'on peut attendre des examens anatomiques, *in vivo*, c'est-à-dire des biopsies qu'on a pu pratiquer à l'occasion des hésitations cliniques.¹

Dans deux cas où nous avons pratiqué la biopsie de la peau et de la muqueuse gingivale, les images de tuberculose folliculaire caséuse et ulcéralive intradermique ou intramuqueuse sont extrêmement typiques sur les coupes. L'existence de formations folliculaires nombreuses permet une distinction anatomo-pathologique de la lésion initiale.

Reste enfin la recherche bactériologique. En règle générale, le bacille de Koch peut être mis en évidence avec la plus extrême facilité dans le pus retiré par ponction de l'adénite tout au moins pendant la première période de l'évolution. On peut aussi, mais moins facilement — la culture et l'inoculation sont souvent nécessaires — prouver l'existence du bacille au niveau de l'ulcération. Cette richesse bacillaire apparaît comme un élément important du diagnostic. Elle contraste nettement avec l'habituelle pauvreté en germe des abcès froids tuberculeux.

En résumé, nous possédons à l'heure actuelle un ensemble de signes cliniques, anatomiques, bactériologiques et immunologiques, qui permettent une description très complète de cette forme spéciale de tuberculose initiale.

A propos du diagnostic bactériologique, il est nécessaire de faire une remarque dont l'intérêt théorique et pratique n'est pas négligeable. Chaque fois qu'on se trouve en présence d'une loca-

¹ La pratique des prélèvements n'étant peut-être pas sans risque ne peut être recommandée.

Étatisation initiale cutanée ou muqueuse l'identification de la variété du bacille (type humain ou bovin) doit être poursuivie.

A vrai dire, par la lecture des observations, nous ne sommes pas bien renseignés sur la variété du germe qui provoque le chancre tuberculeux cutané. Dans notre expérience personnelle qui repose sur un petit nombre d'observations, c'est le bacille humain qui a été isolé. Tout laisse à penser d'ailleurs que c'est lui qui est en cause dans la grande majorité des cas, étant donné l'origine et le mode de contamination très souvent familiale par un tuberculeux pulmonaire.

Sur la race de bacille responsable des tuberculoses gingivo-jugales, nous pouvons apporter notre expérience personnelle. Dans sept cas sur neuf, un bacille bovin — identifié par ses caractères culturels et l'inoculation aux animaux — a été retiré des lésions. Dans deux cas personnels, ainsi que dans une observation de Lelong et de Lebourg et Lambert¹, il s'agit de bacilles de type humain.

Une telle proportion de bacillosés à germe bovin est absolument inconnue dans toute autre variété de tuberculose humaine observée en France, où la fréquence de cette variété microbienne apparaît très réduite. Elle nous engage à rechercher dans l'alimentation la source de la contagion en cas de tuberculose primitive de la bouche. A vrai dire, l'enquête en vue de rechercher l'absorption de lait cru, ou insuffisamment bouilli, ou de fromage, n'a pas toujours été couronnée de succès. Cependant la plupart des enfants qui ont présenté ce type d'accident vivaient habituellement ou occasionnellement à la campagne, dans des fermes et le rôle des poussières rurales bacillifères est à envisager. Il reste encore là une inconnue sur la pathogénie de la maladie.

De même, tout n'est-il pas clair sur le mode de contamination. S'il existe assez souvent une cause locale (carie, abcès dentaire) qui a pu favoriser la localisation, il existe des chancres muqueux de la gencive sans qu'on puisse retrouver la moindre lésion de voisinage. Le rôle si important dans la tuberculose cutanée d'une lésion ou d'un traumatisme préalable, ne ressort donc pas aussi

¹ LEBOURG et LAMBERT, Chancre gingival de primo-infection bacillaire. Soc. Stomatologie de Paris 19 Oct. 1943.

nettement dans l'histoire des tuberculoses initiales de la bouche que dans celle de la peau. On peut faire la même remarque à l'occasion du drame de Lubeck où furent notés des chancres tuberculeux du pharynx, de l'oreille moyenne, de l'intestin, à l'occasion de l'ingestion de bacilles tuberculeux virulents.

CO-RELATOR.

Bronchial Occlusion in Primary Tuberculous Infection.

By **James H. Hutchison**, O. B. E., M. D., M. R. C. P., F. R. F. P. S. G.,
Glasgow, Scotland.

Mr. President, Gentlemen,

It is with some diffidence that I rise to speak on bronchial occlusion in primary tuberculosis in the country of that great bronchoscopist Chevalier Jackson and in the presence of Professor Wallgren whose name is so renowned in connection with this infection. I shall, however, try to draw confidence from the fact that the importance of bronchial occlusion in diseases of the lungs and its occurrence in childhood tuberculosis was first clearly described in 1850 by Sir William Gairdner who was to become professor of medicine in the Glasgow medical school.

In spite of Gairdner's paper the importance of bronchial occlusion in primary tuberculosis was not really appreciated until recent years although the possibility of its occurrence was recognised by Jackson (1930) and others. It has long been known that massive X-ray shadows may appear in the lungs of children passing through their primary tuberculous infection without implying a poor prognosis and without much constitutional malaise. Eliasberg and Neuland described such cases in 1920, regarding the lesion as a non-specific pneumonia in a tuberculous subject, but Reichle (1933) from a study of the histology in their cases gave it as his opinion that the condition was a tuberculous pneumonia without caseation. The most popular conception of «epituberculosis» has been that it is an allergic response around the primary focus although as far as I know such a condition has never been demonstrated histologically in man.

In 1933 Moslock and Pinchin described a case of epituberculosis in which the regional bronchus was obstructed by granulation tissue and in which the X-ray shadow disappeared after the obstruction had been relieved through the bronchoscope. Since then it has been shown by several workers such as Brock, Cann, and Dickinson (1937), Macpherson (1939), Jones, Rafferty, and Willis (1942), and Kent (1942) among others that the extensive X-ray shadow of «epituberculosis» may represent not a pneumonic consolidation at all but absorption collapse of a lobe or sector of lung consequent upon bronchial occlusion. Further, Meneghello and Smith (1943) pointed out that when bronchial occlusion is of the check-valve type obstructive emphysema may occur instead of absorption collapse.

In Glasgow we have investigated a series of 55 cases which would previously have been diagnosed as «epituberculosis» by methods which included X-ray, bronchography, and bronchoscopy. In every case we found evidence of bronchial occlusion. This was shown by bronchoscopy to be due most often to narrowing of the bronchial lumen by the pressure of enlarged tuberculous peri-bronchial glands in combination with sticky mucus produced by a swollen hyperaemic mucous membrane. In some cases a caseous gland had ulcerated through the bronchial wall with the production of granulation tissue within the lumen. Such granulation tissue has been seen to act as a check-valve which by allowing the entry of air into the alveoli during inspiration when the bronchi normally dilate slightly and obstructing its exit during expiration when the bronchi narrow caused ballooning of the air-spaces. Bronchial occlusion with collapse has also been demonstrated by lipiodol bronchography and this method of investigation has revealed also that in this type of absorption collapse as in any other bronchiectasis may develop, although it differs from that due to pyogenic infection in remaining uninfected and more or less symptomless — at least for many months. Bronchial stenosis may also be a rare sequel.

It is usually possible, however, to diagnose bronchial occlusion in tuberculosis without bronchography or bronchoscopy. The paucity of physical signs has frequently been stressed. There is,

however, one sign indicative of bronchial narrowing and frequently found in such cases which has perhaps not received sufficient emphasis although it was first described in 1918 by Jackson. I refer to a history of asthma-like or wheezy breathing or of pertussis-like cough. An «asthmatoïd» wheeze is frequently audible at the open mouth and there may be musical rhonchi over the lungs. So characteristic is this picture that the appearance of «asthma» in a young child, especially in the absence of a family history of allergy, should arouse the suspicion of tuberculous hilar adenitis and indicate the wisdom of doing tuberculin skin tests and having the chest X-rayed. As Jackson (1931) has aptly put it «all is not asthma that wheezes».

Radiographic appearances are not difficult to recognize as a rule with the help of antero-posterior, lateral, and oblique views, but it should be remembered that in these tuberculous cases such classical signs of absorption collapse as mediastinal or tracheal shift, crowding of the ribs, or elevation of the diaphragm are more often absent than present although if the state of collapse persists for a long time they may ultimately appear. They are not present early because in tuberculosis the bronchial lumen is occluded gradually and the slow absorption of air allows the bronchi and alveoli to be filled with reactive exudation of tissue fluid which occurs whenever the bronchi are irritated by bacterial, chemical, or mechanical causes. If this outpouring of fluid outpaces the absorption of air the volume of the affected lobe may be as great as or actually greater than that of the normal lobe.

The radiograph of obstructive emphysema shows an area of increased translucency with possible displacement of the mediastinum to the opposite side. Absorption collapse and obstructive emphysema may be seen to affect the same lobe at different times in any given case.

The right upper and middle lobes are most frequently affected; next in frequency come the left upper and lower lobes; the right lower lobe is least frequently affected. Brock (1946) has pointed out that this incidence can be explained on anatomical grounds. The right mid-lobe bronchus, and to a lesser extent the right upper, left upper, and left lower lobe bronchi are closely sur-

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rounded by the sentinel broncho-pulmonary and tracheo-bronchial glands whereas the right lower lobe bronchus is in less close contact with these glands.

I should now like to show some lantern slides which will illustrate the radiographic, bronchographic, and bronchoscopic appearances upon which a diagnosis of bronchial occlusion is based.

The recognition that «epituberculosis» is in fact absorption collapse raises new problems. What is the place of bronchoscopy in treatment? Is uninfected bronchiectasis secondary to primary tuberculosis common; is it clinically important; is its existence an indication for lobectomy; when should this lobectomy be done? These are problems awaiting the combined efforts of the paediatrician interested in bronchoscopy, the phthisiologist, the thoracic surgeon and the pathologist.

TABLE 1. Incidence of Lobes Affected.

Right upper lobe	11
Right middle lobe	15
Right upper and right middle lobes	1
Right lower lobe	6
Right upper and right lower lobes	1
Right middle and right lower lobes	1
Right upper and left upper lobes	1
Left upper lobe	10
Left lower lobe	8
Left upper and left lower lobes	1

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CO-RELATOR.

Über den Einfluss des Genotypus auf die Tuberkulose-disposition.¹

Prof. Dr. Gerhard Weber, München.

Dass der Genotypus die Disposition für Infektionskrankheiten, die einen Teil der allgemeinen Körperverfassung oder *Konstitution* darstellt, massgeblich beeinflusst, kann als gesichert gelten. Die Konstitution ist aber an den *Phaenotypus* gebunden und hat somit sowohl genotypische als auch peristatische Grundlagen. Den Kliniker interessiert die Frage, in welchem Masse die Disposition des einzelnen Kranken vom Genotypus beeinflusst wird. Dies lässt sich nur feststellen, wenn die Wirkung der Peristase mit ausreichender Genauigkeit abgegrenzt werden kann. Bei den genealogischen Untersuchungen, den statistischen Ergebnissen der Versicherungsgesellschaften und der Zwillingsforschung ist dies nicht möglich. Immerhin haben diese Forschungszweige wichtige Hinweise auf die positive Bedeutung genotypischer Einflüsse ergeben. Allerdings gilt dies fast ausschliesslich für die Tuberkulose der Erwachsenen. Für den Kinderarzt ist die »Altersdisposition« von ausschlaggebender Bedeutung. Wir wissen, dass die Hinfälligkeit in den ersten 3 Lebensmonaten eine fast absolute ist. Einzelne Individuen überstehen aber auch in diesem Lebensalter den tuberkulösen Infekt ohne auffallende Krankheitszeichen. Ich habe die Überzeugung, dass Häufigkeit und Virulenz der Infektion hierbei eine Rolle spielen kann. Auf dem 4. Internationalen Kongress in Rom habe ich über die Bedeutung der »stummen Superinfektion« berichtet. Es besteht aber durchaus die Möglichkeit, dass auch bei diesen Unterschieden im Krankheitsablauf der Säuglingstuberkulose der Genotypus von wesentlicher Bedeutung ist. Eine sichere Aufklärung über diese Frage kann nur der Tierversuch geben, weil es nur so möglich ist, klare experimentelle Bedingungen zu schaffen. Aus einem Tierversuch darf man keine direkten Schlüsse auf die Pathologie des Menschen ziehen. Aufgabe des Experimentes ist es

¹ Broadcasting Copy German.

vielmehr, allgemein gültige Regeln zu finden, die sich dann auch auf den Menschen anwenden lassen.

Bei der Auswahl der Versuchstiere ist von der Fragestellung auszugehen. Will man auf Resistenz untersuchen, muss man eine Tierart von grosser Hinfälligkeit verwenden, denn nur gegen den Hintergrund dieser hohen Speziesdisposition können sich »Plusvarianten« mit genügender Deutlichkeit abheben. Genau das Umgekehrte ist bei Untersuchungen auf »Minusvarianten« erforderlich.

Das als Versuchstier in der Tuberkuloseforschung viel verwendete Meerschweinchen ist bekanntlich durch eine sehr grosse Hinfälligkeit gekennzeichnet. Diese Hinfälligkeit steht so sehr im Vordergrund, dass LENZ diese Tierart überhaupt für ungeeignet hält zum Nachweis erblicher Unterschiede der Tuberkulosedisposition. Eine ähnliche Auffassung vertritt auch v. VERSCHUER. Diese Meinung ist verständlich, da entsprechende Versuche mit Meerschweinchen bisher zu keinem befriedigenden Ergebnis geführt haben. Das gilt sowohl für die Versuche von WRIGHT und LEWIS als auch für diejenigen von KÜSTER und KRÖNING. Wenn man aber nach dem Grunde fragt, weshalb die Versuchsergebnisse dieser Autoren nicht befriedigen, so findet man die Erklärung hierfür ohne weiteres in der Anwendung einer unzumutbaren Versuchstechnik. Abgesehen davon, dass die von WRIGHT und LEWIS verwandten Tierstämme in nicht ausreichendem Masse reingezüchtet waren und bei den Versuchen von KÜSTER und KRÖNING die Infektionsdosis unregelmässig war, wie die Autoren selbst zur Erklärung ihrer ungleichmässigen Versuchsergebnisse angaben, sind in beiden Fällen enorm hohe Infektionsdosen (0.01—0.2 mg Bazillen) verwandt worden, so dass es von vornherein nicht zu erwarten war, dass bei einer so massiven Infektion etwa vorhandene erbliche Resistenzunterschiede überhaupt erkennbar werden könnten. Deshalb war es notwendig, Versuche mit einer verbesserten, exakten Infektionstechnik anzustellen.

In meinen Versuchen verwandte ich die von KRÖNING gezüchteten und auch in den Versuchen von KÜSTER und KRÖNING verwendeten Inzuchtstämme. Die Inzuchtlinien werden nach

einer Mitteilung von KRÖNING über mindestens 20 Generationen fortgeführt. Es wurden 66 Tiere mit der gleichen Infektionstechnik infiziert (Inzuchtstämme XI, XVII und XXII, sowie Kreuzungstiere als Kontrollen). Auf völlig gleiche Umweltbedingungen wurde besonderer Wert gelegt.

Von besonderer Wichtigkeit ist die Technik der Infektion. In Vorversuchen wurde diejenige Infektionsdosis ermittelt, die beim Meerschweinchen gerade noch mit Regelmässigkeit zu einer generalisierenden Tuberkulose mit tödlichem Ausgang führt. Wenn mit sehr kleinen Infektionsdosen gearbeitet wird, wie es bei der Infektion von Meerschweinchen notwendig ist, muss die wirksame Bazillenmenge durch Nährbodenversuch nach dem Verfahren von B. LANGE jedesmal genau festgestellt werden. Wir sind dabei in derselben Weise vorgegangen, wie bei unseren früheren Versuchen (WEBER und DUSCH). Die noch regelmässig wirksame Dosis minima wurde mit 10^{-5} mg feucht gewogenem Bazillenrasen, die ermittelte Keimzahl mit etwa 10 Bazillen festgestellt. Die Infektion erfolgte mit 0.5 cc NaCl-Lösung subcutan. Bei der Beobachtung des Krankheitsverlaufes war das Verhalten des Inzuchtstammes XI besonders auffallend. Die *Tuberkulinempfindlichkeit* trat bei diesen Tieren durchschnittlich später ein, als bei allen anderen Tieren. Die *regionären Lymphdrüsen* wurden häufig gar nicht, sonst später tastbar und führten nur in 2 Fällen zu Abszess- oder Fistelbildungen. Zu einer Zeit, als alle anderen Tiere bereits einen kranken Eindruck machten und stark an Gewicht abgenommen hatten (nach 8—10 Monaten) erschienen die Tiere des Stammes XI noch völlig gesund und nahmen an Gewicht zu. Die *Absterbeordnung* ist besonders eindrucksvoll. Nach Ablauf des 1. Jahres waren alle Tiere verendet mit Ausnahme der Tiere des Stammes XI, die die anderen um durchschnittlich 300 Tage überlebten. Hier zeigt sich deutlich der Erfolg unserer genauen Infektionstechnik im Vergleich mit den Versuchsergebnissen der anderen Autoren. Die *genotypisch bedingte Resistenzsteigerung* tritt mit Eindeutigkeit hervor. Auch die *anatomische Untersuchung* ergab sehr bemerkenswerte Unterschiede bei den verschiedenen Tierstämmen. Bei den Tieren des Stammes XI war die Entwicklung

des Primärherdes bereits weitgehend gehemmt, ja es bestand eine Tendenz zur Ausheilung des Primärherdes. Über die regelmässig erkrankten regionären Lymphdrüsen kommt es zwar zur haematogenen Aussaat in die inneren Organe, die aber ein wesentlich geringeres Ausmass erreicht, als bei den Kontrollen. Leber und Milz bleiben häufig frei oder zeigen nur geringfügige Veränderungen. Auch in der Lunge sind die Herdbildungen weniger zahlreich und haben deutlich die Tendenz zur Lokalisierung und Begrenzung. Ferner ist die Entwicklung von Kavernen bemerkenswert. Die erhöhte erbliche Resistenz äussert sich also hier in dem Übergang der Krankheit von einer subakut verlaufenden, generalisierenden zu einer chronischen, mehr lokalisierten Verlaufsform. Daraus erklärt sich auch, dass bei diesem Tierstamm die Todestermine sich über einen grösseren Zeitraum verteilen, wie bei den anderen, relativ rasch zugrunde gehenden Tierstämmen. Dies ist also nicht ein Ausdruck der »individuellen Variabilität« deren Erhaltenbleiben nach DOERR mit der Annahme einer erblichen Resistenzsteigerung unvereinbar ist, sondern der erbliche Resistenzfaktor führt zu einer chronischen Verlaufsform der Krankheit und mit dieser Verlaufsform ist eine grössere Streuung der Absterbetermini zwangsläufig verbunden. Bemerkenswert war auch das Verhalten der Tiere des Inzuchtstammes XXII, die sich schon während des ganzen Krankheitsverlaufes durch die sehr starke Hinfälligkeit von den anderen Tieren unterschieden hatten. Sie zeigten auch bei der Sektion die schwersten Veränderungen. Besonders auffallend waren die Befunde an den regionären Drüsen, die bei 11 von 21 Tieren in grosse, mit Flüssigkeit gefüllte Höhlen mit dünner, schlaffer Wand umgewandelt waren. Diese kalten Abszesse erreichten Taubenei- bis Walnussgrösse. Dieser Befund wurde ausschliesslich bei Tieren des Stammes XXII erhoben. Es handelt sich also hier um eine *erbliche Organdisposition*. Solche erbliche Organdispositionen konnten bei der Tuberkulose des Kaninchens durch die sehr eindrucksvollen Untersuchungen von K. DIEHL nachgewiesen werden.

Die Vererbung der für die Verschiedenheit der Tuberkulosedisposition verantwortlichen Gene erfolgt unabhängig von äus-

seren Merkmalen, insbesondere der Art der Behaarung und der Haarfarbe. Die gleiche Beobachtung machte auch DIEHL bei seinen Versuchen an Kaninchen. Hiermit stehen die Ergebnisse der Zwillingsforschung (DIEHL und v. VERSCHUER) in Einklang.

Bezüglich des *Erbganges* lassen die beschriebenen Versuche keine Schlussfolgerungen zu. Hierüber können nur Kreuzungsversuche eine Aufklärung bringen, die zwar bereits im Jahr 1938 eingeleitet wurden, aber aus äusseren Gründen nicht zu Ende geführt werden konnten.

Ebenfalls ungeklärt ist noch die Frage, welche praktische Bedeutung die Auswirkung der die Dispositionsvarianten erzeugenden Gene für die Gestaltung des Krankheitsablaufes der Tuberkulose unter natürlichen Bedingungen hat, insbesondere in welchem Ausmass diese Wirkungen durch paratypische Einflüsse gesteigert, abgeschwächt oder gar aufgehoben werden können. Dies können nur weitere, auf die Frage abgestimmte experimentelle Untersuchungen klären. Erst die von uns angewandte Methode ermöglicht aber solche Versuche mit Aussicht auf Erfolg anzustellen. Direkte Parallelen der Tuberkulose des Kindesalters können nicht gezogen werden. Es ist aber anzunehmen, dass der Erbeinfluss beim Menschen mit seiner grösseren allgemeinen Tuberkulose-resistenz sich noch deutlicher bemerkbar macht, als bei einer so hinfälligen Tierart, wie es das Meerschweinchen ist.

Die erbliche Tuberkulosedisposition ist wahrscheinlich eine spezifische und an äusseren Merkmalen nicht erkennbar. Sie geht mit einer allgemeinen unspezifischen Resistenzlosigkeit der Tiere nicht parallel.

Über das Wesen der spezifischen Tuberkulosedisposition brachten Versuche an Kaninchen, die ich mit KIRIMLIDIS ausführte, einige Aufklärung. Es konnte festgestellt werden, dass Kaninchen auf die Bazillen vom Typus *bovinus* anders reagieren, als auf den Typus *humanus*, auch dann, wenn abgetötete Bazillen injiziert werden. Dies spricht dafür, dass die spezifische Empfindlichkeit bis zu einem gewissen Grade von der Lebenstätigkeit der Bazillen unabhängig ist. Ausschlaggebend scheint die spezifische Reizbarkeit der Zellen durch die Leibessubstanzen der Tuberkelbazillen zu sein.

Discussion.

Dr. Luiz Torres Barboza, Rio de Janeiro, Brazil.

I would like to take advantage of the privilege which is conferred on me to take part in the discussion at this session to present in a brief summary the results of the Brazilian 20 years-experience on BCG vaccination in Rio de Janeiro. They represent the work of a group of pediatricians under the leadership of Dr. Arlindo de Assis.

- 1) Since August, 1927, BCG vaccinations have been used in Rio de Janeiro, Brazil, and from that time until May, 1947, 200 000 new born have been vaccinated and it has been possible to follow closely 50 000 of those, up to the present time, through the BCG service (Fundação Ataufo de Paiva).
- 2) In addition, BCG vaccinations were given to 10 000 non-allergic individuals (children older than six months and adults).
- 3) In these 210 000 individuals, the inoculation of BCG proved to be absolutely innocuous.
- 4) The BCG vaccination is administered in Rio de Janeiro only through a specialized service (Fundação Ataufo de Paiva). It is given by mouth in three doses of 30 milligrams each, every 48 hours. The total doses are, therefore, 90 milligrams. The vaccine is given within the first ten days of life; each dose is given before the first morning feeding.

The vaccination is only given to individuals over six months of age after it has been proven that they do not react to tuberculin. This precaution is observed very strictly; not because we believe any harm could result from inoculation of BCG to already allergic individuals, but solely to avoid the possibility of any blame being put on BCG for previously existing tuberculous infection.

- 5) Since February, 1947, the vaccine has been given to children living in proven tuberculous family environment in a different way. For this group, BCG has been administered monthly for five months in 100 milligram doses which makes a total of 500 milligrams.
- 6) The *oral* administration of BCG has been favored in Rio de Janeiro and by this method allergy was obtained in 85 % of the vaccinated individuals. The results depend on the way the vaccine is prepared. It must be freshly prepared from cultures grown in the liquid medium of Sauton, and it is important that these cultures be from 12 to 14 days old in order to assure the maximum vitality of the bacillus (BCG). Experiments carried out in Brazil by Dr. Arlindo de Assis, proved that the dead bacillus does not pass through the intestinal wall and therefore, is not able to produce allergy.

- 7) Investigation of 38 families, where 78 vaccinated children and 74 non-vaccinated children lived together with no special measures of isolation shows: Among the 78 vaccinated, only 1 death from tuberculosis; among the 74 non-vaccinated, 10 deaths from tuberculosis.

These figures represent the results so far obtained with just one administration of vaccine. It is possible that they may have to be revised when more data are accumulated through the inquiries that are being carried out now in a larger number of families.

- 8) We also believe that further experiments and developments will prove that BCG is a still better means of preventing tuberculosis than the present data indicate.

Dr A. Guilbeault, Directeur médical de la clinique BCG de Montréal, Canada:

Mesdames, Messieurs,

Pour protéger avec succès contre la tuberculose par le BCG un enfant naissant dans un foyer tuberculeux, Calmette a prescrit l'isolement complet de ce nouveau-né jusqu'à ce que la réaction tuberculinique devienne positive.

S'inspirant de cette directive, l'honorable Athanase David, ministre de la Santé pour la province de Québec, fonda à Montréal, en 1935, la Clinique BCG. Le Dr Paquette, qui a succédé à l'Honorable David continue de soutenir des deniers publics, la clinique BCG de Montréal.

La Clinique BCG a un double but:

1°) Recevoir, immédiatement après la naissance, des enfants nés dans un foyer tuberculeux et leur offrir un toit les protégeant contre toute infection tuberculeuse pour une période variant de trois à six mois.

2°) Administrer le vaccin BCG à ces nouveau-nés.

En 1935, la capacité de la Clinique était de 9 lits. Des agrandissements ont porté ce nombre à 90 lits.

Après une période d'hospitalisation variant de trois à six mois, les enfants sont remis à leur foyer tuberculeux.

Une fois remis à ses parents, l'enfant est surveillé par le service social. Les infirmières de notre service social, qui font les enquêtes prénatales, revaccinent l'enfant aux âges d'un an, trois ans, sept ans et quinze ans. Une fois par année, elles explorent à la tuberculine, non seulement les enfants qui ont reçu le BCG à la Clinique mais aussi les frères et sœurs qui deviennent ainsi des cas témoins.

L'infirmière visiteuse fait deux visites par an et s'enquiert en même temps de la continuité du contact infectant.

Depuis la fondation de la Clinique en 1935 jusqu'à janvier 1947, 869 enfants ont été hospitalisés à la Clinique BCG.

De ce nombre,

- 57 ont reçu le vaccin BCG per os
- 18 par voie percutanée (méthode de Rosenthal)
- 520 par voie sous-cutanée
- 214 par scarification
- 37 n'ont pas reçu le vaccin
- 19 ont chevauché sur l'année 1947.

En fin d'année 1946, le bilan s'établit comme suit:

- 44 sont décédés, dont un cas de tuberculose
- 26 cas ont été perdus de vue
- 788 enfants sont encore suivis par le service social de la Clinique BCG.

Depuis deux ans, nous avons adopté la vaccination par scarification, faisant usage d'une suspension de bacille dont la concentration est de 75 mg de BCG au cc.

100 % des enfants qui ont été vaccinés par scarification ont une réaction positive à la tuberculine huit semaines après la vaccination quand il n'y a qu'une zone de scarification. La réaction est demeurée positive pour 80 % des enfants qui ont atteint l'âge d'un an.

Considerations personnelles.

1. Une scarification au BCG chez un patient qui a une réaction positive à la tuberculine donne les résultats suivants:

Si la positivité de la réaction est exclusivement due à l'absorption antérieure du BCG, la réaction locale est de peu d'intensité. Au contraire, la réaction locale devient très forte et persiste de trois à huit semaines si la positivité de la réaction est due à la présence de bacille de Koch, ou encore, de bacille de Koch et du vaccin BCG.

Ce sujet est à l'étude et peut devenir un moyen précieux pour identifier la cause de l'allergie tuberculinique.

2. Le bacille BCG, *in vivo*, est très sensible à la streptomycine. Ce médicament peut faire virer la positivité de la réaction à la tuberculine. Dans un tel cas, nous recommandons la revaccination.

La mortalité tuberculeuse chez les sujets hospitalisés et vaccinés à la Clinique se résume à un enfant, mort de tuberculose généralisée, dans des circonstances qui méritent d'être relatées:

L'enfant P naît d'une mère tuberculeuse à l'hôpital du Sacré-Cœur. Immédiatement après sa naissance, il est éloigné de sa mère et transporté à la Clinique BCG.

Le 9^e jour après sa naissance, il reçoit le BCG par la bouche en même temps que trois autres nouveau-nés.

Huit jours après la vaccination, il meurt de tuberculose généralisée confirmée par l'autopsie. La culture du bacille révèle un bacille tuber-

culeux type humain. La mère décède à l'hôpital du Sacré-Cœur deux mois après la naissance du bébé. L'autopsie de la mère révèle une lésion caséuse importante de l'utérus. La tuberculose de la mère est du type humain. Il s'agit ici d'une tuberculose *Transplacentaire*.

Si nous considérons la mortalité par tuberculose chez des enfants qui ont reçu le BCG avec isolement spécial et qui, trois mois après avoir été vaccinés, ont vécu en contact avec des tuberculeux, nous n'avons aucune mort par tuberculose à rapporter.

Pour ce qui est de la morbidité tuberculeuse, un seul enfant développe une atteinte du parenchyme pulmonaire. Il s'agit d'une fillette de sept ans, vivant en contact, depuis son départ de la Clinique, avec son père qui souffre de tuberculose ulcéro-fibreuse, dont les crachats sont positifs et qui n'observe aucune mesure hygiénique.

En septembre prochain, le Conseil National des Recherches au Canada étudiera en détail chaque dossier et établira des statistiques sur les enfants qui ont reçu le BCG avec isolement à la Clinique BCG.

La Clinique BCG fait plus que s'intéresser aux enfants naissant dans des foyers tuberculeux. Nous croyons que l'excellence des résultats est due, non seulement à l'isolement mais aussi à la pratique des revaccinations.

Dans la province de Québec, d'après les chiffres fournis par le Dr. Frappier, directeur de l'Institut de Microbiologie de l'Université de Montréal, 20 % des nouveau-nés reçoivent le vaccin BCG à la naissance.

En collaboration avec le Dr. Frappier, le service social de la Clinique BCG a entrepris de revacciner, à l'âge d'un an, les enfants du district de Montréal.

Ainsi, d'avril 1946 à avril 1947, 2 505 enfants ont reçu la revaccination d'un an.

Ici encore, l'infirmière visiteuse ne s'intéresse pas seulement à l'enfant qu'elle doit revacciner. A une première visite, elle fait subir l'épreuve à la tuberculine à tous les enfants de la famille.

Ainsi, dans 2 792 familles visitées, il y a 7 036 enfants dont 6 314 ont subi l'épreuve à la tuberculine.

Resultats.

Petit à petit, depuis douze ans, la Clinique BCG de Montréal a pu mettre au point un organisme pour la protection contre la tuberculose par le vaccin BCG, de l'enfance d'âge pré-scolaire d'une ville dont la population touche le million.

1. Vaccin BCG administré avec isolement spécial aux enfants nés en milieu tuberculeux.

2. Vaccin BCG administré à domicile par l'équipe volante des infirmières visiteuses pour vaccination en milieu sain.

3. Revaccination en milieu de toute qualité.

Ce travail est le fruit, non pas d'un seul homme, mais de tout le personnel de la Clinique, de la haute qualité du vaccin BCG préparé sous la surveillance du Dr. Frappier, à l'Institut de Microbiologie de l'Université de Montréal et à la profonde conviction qu'ont le bureau d'administration de la Clinique et le Ministère de la Santé de la province de Québec, que nous faisons œuvre utile.

Dr. **Gian Pietro Ravera**, Turin, Italy: *An index of virulence in experimental tuberculosis in Guinea pigs.*

The purpose of this communication is to call the attention of the medical profession to the subject of this valuable index of virulence devised to measure quantitatively the degree of toxicity of a non-specific virus injected into an experimental animal.

Substantially this index shows the following:

The virulence is higher in direct relation to the rapidity of death.

The virulence also bears a direct relation to the rapidity of weight loss of the injected animal, as compared to the control.

The limits of variability of the index are between 0 and 1, and intermediate values give the measure of the different degrees of virulence.

For example, if the inoculation is made from a culture, an index of 0.60—0.65 may be obtained; whereas if the inoculation is made from a tuberculous exudate a value of 0.90—0.92 is usual.

I have been able to prove that such numerical values are constant according to the mode of inoculation with the exception of differences due to the individual resistances of the experimental animals.

K. **Choremis**, M. D., Athens, Greece: *On streptomycin therapy of tuberculous meningitis.*

It is only after the first days of last April that we were able to start streptomycin therapy in our hospital. Our experience extends to half a score of cases of tuberculous meningitis, either uncomplicated or in combination with miliary tuberculosis (Cases 2 and 7). The two cases last mentioned are still under treatment. Our report thus covers a period of approximately 3 months of streptomycin therapy. The series includes those children who began treatment up to the end of May.

Because our supply of streptomycin was limited, the usual dose was 1 gram per day, of which 0.10 gm was given into the spinal canal and the rest in 8 equal doses intramuscularly every 3 hours.

In this series of 10 cases, regression of the disease has been observed. Streptomycin therapy modifies the course of tuberculous meningitis in several typical respects. Thus, we have observed in the early stages an intensification of the manifestations of meningitis, the spinal fluid

protein content and cell count being increased, sometimes to high levels. The sugar and chloride concentrations are not affected. At this stage, one frequently notices also a *regression of the patient's general condition*. While these phenomena of aggravation of the inflammatory process appear soon after treatment is started, favorable effects on the patient's general condition and on the findings in the cerebrospinal fluid are rather slow and are usually observed after the 15th day.

In four cases the rising curve of cerebrospinal fluid sugar crossed the descending curve of the protein level as the patient improved. The sedimentation rate of red blood corpuscles, originally high, began to fall gradually in some instances, while in others it underwent a temporary increase with treatment, subsequently dropping off to lower levels.

The behavior of the *skin allergic phenomena* is noteworthy. Under the effect of streptomycin therapy the site of an earlier Mantoux test, originally recorded as negative or weakly positive, would blossom with a positive reaction. Additional tests, placed at other sites, showed an increase in the response, with a larger area of induration, greater intensity of coloring, and more prolonged duration. This increase in sensitivity seems to apply exclusively to the skin, since the tuberculin reaction of these patients is not influenced by mixing their serum with the tuberculin used for testing.

Toxic phenomena referable to intramuscular injections of the drug were either absent or insignificant. Twice we have seen a transitory erythema which, of course, did not call for interruption of the treatment. At the same time, we must call attention to certain unpleasant phenomena which follow intrathecal injection of the drug. The usual precautions were observed: 0.10 gram of streptomycin was dissolved in 10 cc of physiological saline, and the solution was injected only after withdrawal of 5 cc or more of cerebrospinal fluid. In spite of these measures, convulsions and fever frequently occurred. Four of our young patients exhibited rigidity of the neck and back, and one of them developed such a degree of opisthotonos that he found relief, when quite clear mentally, in remaining for many hours supported on his occiput and heels. These phenomena compelled us to admit the irritating property of intrathecal injections of streptomycin and caused us to administer them at first only every other day and with great caution. Gradually the spinal infusions were still further spaced. In one case, in a girl of 8 years with thoracic Potts disease dating from the age of 3½ years, intrathecal injection of streptomycin was thought to have provoked an obstruction of the spinal canal; cerebrospinal fluid removed from the lumbar region, as compared with simultaneous samples obtained by cisternal puncture, was under lower pressure and contained a higher cell count and higher protein concentration.

Confirmation of the irritating effect of streptomycin when adminis-

tered intrathecally was obtained by injecting 0.10 gm of streptomycin into the spinal canal of a mentally defective subject whose spinal fluid had previously been found to be normal. The injection was followed by chills and convulsions, and by elevation of the spinal fluid pressure, cell count (500 polynuclears) and protein content.

Under the effect of therapy all of our patients gained weight. The improvement in their general appearance was even more striking. Many of the symptoms of disease likewise disappeared. Thus, vertigo and headache diminished, except for temporary aggravation following intraspinal injection of the drug. Constipation likewise abated, at a slow rate. Indeed, in none of these children was distension of the abdomen observed, though it is usual in tuberculous meningitis. No pathological findings occurred in the urine. It is our impression that streptomycin therapy has had a favorable influence on the roentgen picture in these patients. This has been particularly noteworthy in the two cases of miliary tuberculosis, which were also free from pulmonary symptoms or physical signs.

We have studied the concentration of lipase in both the blood and cerebrospinal fluid of our patients. In general, it may be stated that the cerebrospinal fluid lipase is constantly increased in tuberculous meningitis, but that its level falls with streptomycin therapy, fluctuating between 0.20 and 0.50 units. The blood lipase concentration presents no constant changes.

Improvement in the eyegrounds followed therapy rather promptly. The alterations found, which consisted of bilateral areas of congestion, more or less sharply demarcated, disappeared under observation.

Streptomycin treatment has in our hands been supported by injections of ascorbic acid and graded amounts of tuberculin.

In three of the patients in our series the cerebrospinal fluid has become normal.

M. Weill-Hallé, Paris, France.

Mesdames, Messieurs:

L'amabilité de notre Président me permet une courte intervention. Vingt-six ans ont passé depuis que j'ai procédé à la première application à l'espèce humaine du vaccin de Calmette-Guérin, le B. C. G.

En 1926, au nom d'Albert Calmette et de moi-même, j'apportais à la 22nd réunion de l'Association Nationale de la Tuberculose à Washington, la relation encore bien modeste, mais pleine d'espoir, de nos premiers essais de vaccination.

En dépit de maint préjugé, et grâce à l'appui de bien des travaux étrangers, de la Scandinavie au Canada, de la Yougo-Slavie à l'Amérique latine, le B. C. G. a triomphé.

La semaine passée, j'ai rencontré dans ce pays deux des plus dis-

tingués expérimentateurs du B. C. G.: d'abord J. D. Aronson du Phipps Institute du Philadelphia; et puis S. R. Rosenthal du Tice Laboratory qui n'avait invité à assister à la signature, par le Gouverneur Green de l'État l'Illinois, d'un bill garantissant la fondation à Chicago de la maison du B. C. G. qui assurera la préparation, l'application et la diffusion du vaccin dans tous les États-Unis.

Et maintenant, pour être bref, puis-je solliciter le Président de proposer au Congrès d'adopter les conclusions des distingués rapporteurs favorable à la vaccination.

Je veux informer tous nos collègues que nous préparons une conférence internationale qui se tiendra l'an prochain à Paris.

Cette conférence, à laquelle ils sont invités à apporter leurs statistiques, conclusions et éventuellement leurs objections, aura pour but d'établir une entente sur les méthodes d'application et de contrôle de la vaccination au B. C. G.

Je veux espérer que cette conférence aura pour effet de réduire largement les souffrances physiques et morales imposées à tant de malheureux, surtout en Europe, par ce fléau, encore vaincu, la tuberculose.

Prof. A. F. Tour, membre-correspondant de l'Académie des Sciences Méd. de l'URSS: *Essai de vaccination BCG en masse en URSS.*

La vaccination antituberculeuse des nouveau-nés, proposée par Calmette, souleva un vif intérêt non seulement au milieu des savants, mais aussi dans les sections du Commissariat du peuple à la Santé publique et reçut bientôt une grande application pratique. De nombreuses épreuves, précédées par les expériences laboratoriens avec des animaux, puis la surveillance clinique sur les enfants vaccinés largement menée en Ukraine, à Moscou, à Leningrad et dans beaucoup d'autres grandes villes de l'Union, ont permis au Commissariat à la Santé publique (à présent — le Ministère à la Santé publique de l'URSS) de réglementer en 1942 par décret «la vaccination antituberculeuse obligatoire pour tous les nouveau-nés, dans toutes les maisons d'accouchement».

La vaccination des nouveau-nés se fait dans les maisons d'accouchement. Le vaccin se donne le plus souvent per os dès l'âge de 3—5 jours, une fois dans deux jours, trois fois de suite. Les contre-indications à la vaccination de l'enfant sont peu nombreuses: 1) non-viabilité du nouveau-né, 2) l'augmentation de température au delà de 37.5°, 3) les phénomènes aigus de dyspepsie, 4) les courts vomissements tenaces, 5) les autres maladies qui troublent l'ensemble de l'état de l'enfant — pneumonie, septicémie, procès purulents etc. La pratique a montré qu'il n'existe aucun motif pour détourner de la vaccination préventive les enfants nés avant terme, dont le poids de naissance est bas, s'ils sont tout à fait viables.

Les enfants qui, pour quelque raison, n'ont pas reçu le vaccin BCG

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pendant leur séjour dans la maison d'accouchement, sont soumis à la vaccination plus tard, dans le bureau de consultations de nourrisson de l'arrondissement.

On porte une attention toute particulière aux cas de vaccination des nouveau-nés sortant du milieu tuberculeux. Un travail conforme se mène dans cette direction — par le dispensaire antituberculeux, le bureau de consultations de nourrisson, les maisons d'accouchement et le bureau de consultations maternelles.

Le dispensaire antituberculeux informe le bureau de consultations de nourrisson de la quantité de femmes enceintes, atteintes de tuberculose, ou vivant en proche contact avec les malades.

Le bureau de consultations maternelles, à son tour, dirige ces femmes chez le spécialiste-phtisiateur, surtout dans les cas, où les données cliniques ou anamnétiques manifestent dans leurs affections la possibilité de l'étiologie tuberculeuse.

Ainsi l'accouchée entre dans la maison d'accouchement bien examinée, munie des données de toutes les investigations cliniques, laboratorielles et celles de Roentgen, ce qui permet de garantir les mesures prophylactiques, médicales et épidémiologiques à la mère et au nouveau-né dans la maison d'accouchement, de même qu'à domicile.

Les mesures strictes sont prises pour l'isolation complète du nouveau-né, vacciné BCG pendant $1\frac{1}{2}$ —2 mois de sa mère bacillaire ou de son entourage tuberculeux. Si la mère est saine elle peut être envoyée avec son enfant dans la maison de repos de la mère et du nouveau-né, autrement les tuberculeux de son milieu doivent être mis pour cette période au sanatorium ou à l'hôpital.

La maison d'accouchement, faisant passer le nouveau-né sous la surveillance du bureau de consultations de nourrisson, envoie en même temps au personnel médical toutes les informations, touchant la santé de la mère, le contact tuberculeux, s'il en existe, les données de la vaccination, si elle a eu lieu, ou les raisons qui l'ont retardée. Les nouveau-nés, dont les mères sont atteintes de tuberculose, ou qui sortent d'un milieu tuberculeux, se dirigent immédiatement sous la surveillance d'un phtisiateur spécial du bureau des consultations de nourrisson.

Périodiquement on fait subir aux enfants vaccinés ainsi qu'aux enfants non-vaccinés la réaction Pirquet. On estime, quoique à l'heure qu'il est, avec quelques limitations, que la faible réaction de Mantoux avec la réaction négative Pirquet démontre l'allergie post-vaccinale. L'épreuve cutanée positive pour la plupart des cas démontre chez l'enfant l'infection de tuberculose. Ces enfants se dirigent sous la surveillance particulière de phtisiateur.

Au moment actuel, l'Union Soviétique a accumulé les résultats d'une énorme pratique. A peu près trois millions d'enfants nouveau-nés ont été vaccinés, ce qui permet de faire des conclusions bien nettes.

La première question qui se pose devant nous: La vaccination, est-elle effective? Y-a-t-il assez de raisons pour l'introduire dans le système des mesures employées pour la protection de l'enfance?

La réponse à ces questions ne peut être que tout à fait affirmative. Les données de statistique de morbidité et de mortalité à cause de tuberculose, l'écoulement des procès tuberculeux chez les enfants vaccinés, ainsi que chez ceux non-vaccinés, du milieu tuberculeux bacillaire nous le démontrent.

Les observations de longue durée, menées scrupuleusement par ADELBERG (Leningrad) faites en considération de toutes les conditions de vie et de particularités du contact tuberculeux, dont le rôle important fut souligné avec raison par ALDERCHOFF, ont montré que la mortalité générale des enfants du milieu tuberculeux durant la première année de leur vie a été diminuée en 2 fois et la mortalité à cause de tuberculose est devenue en 3.5 fois moindre que celles du groupe de contrôle, dont les enfants n'avaient pas été vaccinés. Durant la seconde année la mortalité générale parmi les enfants vaccinés était à peu près la même que parmi les enfants du groupe de contrôle, tandis que la mortalité à cause de tuberculose moindre en 3.2 fois. Ces données, reçues à Leningrad par ADELBERG en période de 1928 jusqu'à l'an 1934 ont été confirmées par les observations plus récentes (de 1936—1938) menées par elle en commun avec VOLTCHOK.

D'après les investigations de CHOURIGINA (Moscou, 1928—1931) la tuberculose locale chez les enfants vaccinés a donné 4.3 %, tandis que chez les enfants non-vaccinés — 18 %. Parmi les enfants vaccinés qui se trouvaient en contact avec les malades bacillaires 0.6 % étaient morts durant une année. Parmi les enfants de contrôle — 9 %. ROYSMAN et KAMENETSKAYA (Odessa) qui surveillaient durant 5 ans les enfants vaccinés et les enfants non-vaccinés, sortant du milieu tuberculeux, notent que parmi les premiers 10 % étaient atteints de tuberculose et 2.9 % étaient morts, parmi les autres 29.3 % étaient atteints et 7 % étaient morts.

JAKNITCH (R. S. S. d'Ukraine), NOVOCELSKY avec ses collaborateurs (Leningrad) et beaucoup d'autres dénotent des données analogues.

KLEBANOFF cite les résultats suivants de la vaccination BCG des nouveau-nés en masse à Moscou en 1938. De 10 000 nouveau-nés, la première année — 12.3 % des enfants vaccinés étaient mort de tuberculose. De 10 000 nouveau-nés non-vaccinés — 21,8 % étaient morts. Pendant la deuxième année de 10 000 enfants vaccinés 10.4 % étaient morts, de 10 000 enfants non-vaccinés deux fois autant — 20.8 %.

Très démonstratifs sont les résultats obtenus à Leningrad de 1927 jusqu'à l'an 1945. La vaccination des nouveau-nés en masse fût commencée en 1937. Si on prend pour la mortalité provoquée par tuberculose la première année de vie pour 1 000 enfants nés en 1927, relative-

ment le chiffre 100 — on verra d'après le diagramme obtenu depuis lors, qu'en 1937 elle s'est réduite à 70, en 1938 — à 62, en 1939 — à 50, en 1941 — à 33 et en 1942 — à 12.

Il est évident, qu'une forte influence sur l'abaissement de la mortalité provoquée par tuberculose eut l'amélioration, progressive des conditions de vie de larges masses à Leningrad, de même qu'une large assistance médicale sanitaire et les autres moments sociaux, mais il n'y a pas de doute que l'influence principale doit être attribuée à l'effet immunisateur des vaccinations antituberculeuses d'après CALMETTE.

Beaucoup d'auteurs russes, comme nous voyons dans les données citées plus haut par ADELBERG, notent l'abaissement de la mortalité parmi les enfants vaccinés non seulement de tuberculose, mais de même des autres maladies — ce que confirme l'opinion de Calmette, que le vaccin BCG produit l'effet immunisateur paraspécifique.

On peut juger des résultats de vaccination d'après les particularités du cours du procès tuberculeux chez les enfants vaccinés et non-vaccinés. VOLTCHOK et ADELBERG (Leningrad) constataient chez les enfants vaccinés l'issue favorable — résolution ou organisation des infiltrats pulmonaires en 1.5 fois plus souvent, et l'issue défavorable — procès caséux et dissémination en 4 fois plus rare, que chez les autres. Les auteurs indiqués ci-dessus constataient chez les enfants vaccinés en 8.6 % des cas la calcification du complexe tuberculeux, ce que chez les enfants non-vaccinés ne se rencontrait pas.

Les métastases extra-pulmonaires chez les enfants vaccinés se rencontrent plus rarement que chez les enfants non-vaccinés et portent le caractère beaucoup plus favorable. On constatait chez les nouveau-nés vaccinés — les tuberculides, scrofuloderme, spina ventosa; chez les enfants non-vaccinés — la tuberculose des ganglions périphériques lymphatiques, tuberculose des os et des jointures et la kératite tuberculeuse.

Les résultats positifs de la vaccination antituberculeuse des enfants s'expliquent par l'acroissement, grâce à elle, de l'immunité, liée, il faut croire, avec l'apparition de l'allergie spécifique.

Cependant il faut noter que les investigations de la clinique tuberculeuse de l'Institut Pédiatrie de Médecine de Leningrad montrent, que l'immunité antituberculeuse après la vaccination BCG a lieu même avec les réactions allergiques négatives (VOLTCHOK).

La seconde question se pose devant nous: — La vaccination BCG antituberculeuse, est-elle parfaitement inoffensive pour l'enfant? est-il possible qu'en résultat elle peut provoquer la tuberculose et d'autres complications et conséquences défavorables?

C'est seulement après avoir obtenu une réponse définitive à cette question, que nous pouvons admettre la possibilité de vaccination antituberculeuse en masse.

Les investigations expérimentales de TERASSEVITCH, ZEKHNOVI-

TCHER, ELBERT, ADELBERG, BOGOSLOVSKAIA, SAVCHINSKY et des autres auteurs russes ont confirmé les résultats des observations de Calmette, que les bacilles Calmette-Guérin ne sont pas pathogènes. Les investigations de LEVITANE et LOKHOFF avec les singes ont démontré que le vaccin BCG est tout à fait inoffensif pour les singes et sa virulence ne s'accroît pas ni sous l'influence des injections répétées, ni sous l'influence des maladies d'hasards et des conditions défavorables de vie (VOLTCHOK).

Les investigations très intéressantes de BELANOVSKY avec les cultures des lymphacites de l'homme parlent aussi de l'innocuité et de l'effet immunisateur de BCG.

Nos observations cliniques de longue durée des nouveau-nés à la période de vaccination et durant les semaines et les mois qui succédaient, ainsi que les observations des autres clinicistes: ADELBERG, VOLTCHOK, MEDOVIKOFF, KLEBANOFF et de beaucoup d'autres montrent que l'injection du vaccin per os et sous la peau ne produit chez les enfants aucune réaction générale — ne s'accompagne pas d'augmentation de température, des dérangement d'estomac et des intestins ou d'autres phénomènes négatifs objectifs ou subjectifs.

A ce qu'il paraît, à l'âge de 2—3 mois certains enfants, qui avaient subi la vaccination, peuvent donner le grossissement temporel des glandes bronchiques accompagné quelques fois par la température subfébrile de longue durée, mais n'ayant aucune influence sur l'état de la santé et la courbe de poids.

Si la vaccination se fait sous la peau, ce qui s'appliquait largement à Leningrad, assez souvent à peu près dans 30 %, deux mois après la vaccination apparaissent les infiltrats sous-cutanés. Dans 83 % ces infiltrats se résolvent et dans 17 % ils donnent une pyogénie, qui s'écoule chez les enfants sans augmentation de température et sans autres phénomènes généraux. Ces infiltrats, d'après les observations de LOKHOFF, sont des foyers typiques de tuberculose et doivent être considérés comme le dépôt d'antigène (VOLTCHOK). L'apparition de ces foyers ne peut être en aucune manière la raison suffisante pour renoncer à la vaccination antituberculeuse en masse, mais en choisissant la méthode d'injection, il faut y payer une attention nécessaire.

Ainsi l'efficacité incontestable de la vaccination antituberculeuse pour les enfants, l'absence complète de toutes conséquences négatives immédiates ou distantes ont donné aux autorités de la protection de la santé publique le droit d'introduire dès l'an 1942 l'immunisation obligatoire de tous les nouveau-nés d'après la méthode Calmette. Les raisons purement techniques ne permettent pas, au moment actuel, d'introduire cette mesure partout et la limite principalement par des grandes villes des Républiques de l'Union.

Cependant les questions théorétiques ainsi que celle d'organisation de la vaccination BCG en masse chez nous ne se considèrent pas définitivement déterminées.

Les observations ultérieures à l'intention d'élucider la question de la méthode la plus efficace de la vaccination se prolongent sans interruption. D'après les données cliniques de MEDOVIKOFF la méthode sous-cutanée ne s'est pas montrée plus efficace que celle per os. Les investigations expérimentales d'ADELBERG parlent de la même efficacité de vaccination par la méthode sous-cutanée et la méthode entérale répétitive. D'après ROSENBERG, qui travaillait avec les animaux d'expérience (les lapins et les cobayes) — la meilleure immunisation s'obtient par la méthode combinée «simultanée» par injection du vaccin BCG de la manière sous-cutanée-entérale. La méthode de vaccination cutanée mérite une étude plus largement menée.

On mène les travaux ultérieurs à l'intention d'obtenir les vaccins les plus persistants; on est parvenu à obtenir un vaccin sec suffisamment actif, mais il faut encore exécuter de scrupuleuses investigations des qualités immunogènes de différents vaccins, liquids et secs, et vérifier leur comparative efficacité sur les enfants.

Parmi les mesures d'organisation, qui exigent un plus large développement il faut citer la question de la revaccination et de l'immunisation primaire des enfants plus âgés.

Dans ces directions nous possédons les résultats d'assez nombreuses et scrupuleuses investigations. Les observations cliniques menées par CHOURIGINA, FERTIK et les autres prouvent l'efficacité et l'innocuité de revaccination pour les enfants. La revaccination de même que la vaccination primaire ne provoquent chez les enfants qu'une réaction insignifiante de côté des ganglions lymphatiques et de l'hémogramme (monocythose, eosinophilia). La question de termes conformes au but de revaccination n'est pas encore résolue. Apparemment la nécessité se révèle vers la fin du premier an, ou au commencement du second an de la vie. Il faut admettre, que la première revaccination est désirable depuis l'âge d'un an jusqu'à 3 ans. La seconde — de 4 à 7, et la troisième — de 8 à 12, la quatrième après 13 ans.

Ménée largement et avec succès depuis beaucoup d'années, la vaccination des nouveau-nés a naturellement mis en avant la question d'immunisation des enfants plus âgées et des adultes. (BAYLIN, BERLINE, KLEBANOFF, MOROSOVSKY, RABOUKHINE, KHMELNITZKY et les autres.) Même à présent, comme un expériment clinique, largement mené à Moscou, Leningrad et plusieurs autres villes de l'Union, a lieu l'immunisation primaire des tout-petits enfants, des prescolaires, des écoliers et des adolescents. L'attention toute particulière se prête à la vaccination des enfants, sortis d'un milieu tuberculeux. Certes, les enfants, chez qui la réaction à tuberculine est positive, s'écarte de la vaccination BCG.

Il y a toute raison de croire, que la vaccination des enfants d'un certain âge recevra bientôt chez nous l'étendue et la forme d'une mesure prophylactique en masse et donnera les mêmes résultats positifs, que ceux de l'immunisation des nouveau-nés.

Il est bien évident, que l'étendue de la prophylaxie spécifique de tuberculose au milieu de la population infantine, n'ôte pas et même ne limite non plus la nécessité d'un large développement des mesures prophylactiques ordinaires, non-spécifiques, de même que les mesures d'organisation pour lutter contre la tuberculose.

La nécessité de toutes ces mesures provient du fait, incontestablement établi, que l'efficacité de la vaccination antituberculeuse des enfants dépend en grande partie de la massivité du contact tuberculeux, des conditions de vie et des conditions sociales du milieu.

On peut croire, que la vaccination antituberculeuse BCG est entrée solidement dans le système des mesures de protection de la santé des enfants, si largement et heureusement déployées dans notre beau pays.

Leningrad, le 1^{er} Mai 1947.

Leonardo de Castro Freire, Lisbonne, Portugal: *La streptomycine dans les manifestations graves de la tuberculose infantine.*

Le Portugal s'est naturellement intéressé, avec enthousiasme, sur les possibilités de la streptomycine dans la tuberculose, dès les premiers essais et espoirs. On s'est rué, comme partout, sur les granulies, la broncho-pneumonie caséuse et sur la méningite, formes reconnues comme spécialement graves, fatales; on a vu, dès le début, qu'on était tombé sur quelque chose de différent des tentatives précédentes, qui, toutes, avaient échoué, puisque, dans une partie des cas, au moins, on a constaté que les enfants ne mouraient pas dans le délai habituel.

Notre statistique n'est pas grande, vu la quantité réduite de streptomycine qu'on peut se procurer au Portugal, mais ce n'est pas seulement le nombre de cas qui compte. Nos essais ont été et continuent d'être à tâtons, vu que des indications sûres n'existent pas encore, surtout par rapport aux applications intrarachidiennes de la streptomycine. Pour les applications intramusculaires nous n'avons pas dépassé 50 000 à 100 000 u. par kilo de poids et par jour, en 6 injections quotidiennes. Nos résultats sur les manifestations pulmonaires de la granulie sont très satisfaisants. Dans un cas, de granulie pulmonaire avec bacilles dans le suc gastrique à jeun, guéri en cinq mois, la streptomycine intramusculaire toujours continuellement administrée, n'a pas pu empêcher de se produire une méningite, à B. K. positifs dans le liquor, au bout de trois mois. Cette observation, comme bien d'autres, connues de beaucoup de pédiatres, nous a prouvé que le traitement efficace de M. T. doit être intrarachidien.

Dernièrement nous soignons nos M. T. simples, sans granulies pulmonaires, seulement par voie intrathécale; nous adjoignons naturellement le traitement intramusculaire quand il y a des localisations tuberculeuses importantes ailleurs; nos résultats n'en sont pas moins bons et en plus cela nous fait une importante économie en streptomycine.

Par voie intrarachidienne nous n'allons jamais au-dessus de 200 000 u. quotidiennes, en une ou deux injections par jour. Puis, peu à peu, selon l'évolution du cas, on baisse les doses et on espace les ponctions jusqu'à 25 000 u. une fois par semaine.

Avec ces doses nous n'avons jamais eu de réactions graves, voir de l'amaurose, de la surdité ou des altérations psychiques chez nos petits malades, imputables à la streptomycine. Les maux de tête et vomissements sont des premiers symptômes que nous voyons disparaître. Les enfants, déjà en voie nette d'amélioration, gardent pendant longtemps, pendant des mois de la fièvre, des signes cliniques plus ou moins discrets et des signes évidents à l'examen du liquor: hyperalbuminose, pléocitose à prédominance de lymphocytes, réactions positives de Waltner, de la Triptophan etc.; toutefois, voit-on une tendance précoce du sucre à monter vers les valeurs voisines de la limite inférieure de la normale.

Dans deux cas de notre service, soignés depuis plusieurs mois, les analyses marchent déjà vers la normale; on serait presque tenté de parler de guérison.

Les cas à bacilles de Koch positifs deviennent rapidement stériles et ceux à B. K. négatifs, mais avec inoculation positive ont eu, par la suite, plusieurs inoculations négatives.

La plupart des enfants qui ont dépassé, de beaucoup, la période de mort probable sans traitement, n'ont plus de douleurs de tête, ni vomissements, mangent, augmentent de poids, s'amuse et marchent d'une marche titubante, à jambes écartées, un peu ataxique aussi, mais avec tendance à amélioration par la suite. La fièvre chez ces quelques cas devient moins intense et finit par tomber.

Mais nous savons que tous les cas ne s'améliorent pas de la sorte.

Nous avons soigné dans notre service jusqu'à présent 15 cas de méningites et méningites accompagnées de granulie avec 4 cas de mort. Le premier enfant âgé de 10 mois dont la méningite avait cliniquement débuté, six jours avant son entrée à l'hôpital, par une forte convulsion, nous est arrivé dans un état très grave, presque en coma, est mort 24 heures après et n'a eu que 2 injections intrathécales de 100 000 u. Deux autres cas, âgés de 3 ans et 16 mois sont venus à l'hôpital, après 12 à 15 jours d'évolution méningitique et les deux en état grave d'intoxication et d'exicose: ces deux petites sont mortes, l'une 2 jours, l'autre 8 jours après avoir initié le traitement. Ces deux cas ont été autopsiés; l'un avait une pure méningite, l'autre une vraie granulie méningienne du cortex cérébral et du cervelet. L'examen minutieux n'a montré aucune lésion différente des lésions classiques, imputable à la streptomycine.

Le 4^{ème} cas de mort de notre service, garçon de 6 ans, malade depuis une douzaine de jours, nous est aussi arrivé dans un état très grave, presque en coma; il est mort à la maison quelques jours après la sortie de l'hôpital. Donc, dans les cas très avancés, on a très grave allure, surtout chez les très jeunes enfants, dont l'atteinte des centres du métabolisme

et des centres bulbaires est précoce et intense, la streptomycine est à notre avis, inopérante, du moins dans beaucoup de cas.

D'autres cas, même après une amélioration considérable, entrent dans une phase chronique, d'aggravation lente, parfois avec des symptômes où l'on peut penser à des lésions d'encéphalite (rigidité, contractions permanentes, agitation, soubresauts musculaires, etc.); ils sont voués à la mort ou à une encéphalite chronique, certainement catastrophique, dont on ne connaît pas encore ni les cadres, ni l'évolution.

Restent les enfants dont nous avons déjà parlé, qui, dans un état d'amélioration remarquable avec 4, 5, 6 mois et même un an de survie, d'après quelques cas rares déjà publiés, dans d'autres pays, quelques uns, qu'on croyait presque guéris, sans fièvre, les uns avec réactions importantes du liquor, d'autres sans réactions, ou des réactions très légères; que faut-il en penser? quel est leur destin? que faut-il en faire? Nous savons qu'abandonnés, sans traitement à longue échéance, une grande partie retombe dans la maladie, font des rechutes fatales et n'étaient vraiment que dans un état de guérison latente. C'est se croire ce que les nombreuses statistiques qui vont être bientôt publiées, nous montreront. Mais ne sera-t-il pas possible, en faisant subir à ces enfants, des traitements modérés à longue échéance, avec des périodes de repos, d'en sauver quelques uns au moins?

Dans notre service ces cas suivront deux lignes de conduite: les uns feront une injection intrarachidienne de 25 000 ou 50 000 u. une fois par semaine, les autres feront une semaine de traitement par mois à base de 50 000 u. intrarachidiennes une fois par jour. L'expérience nous montrera si nous sommes dans une bonne voie ou s'il faut faire des traitements plus intenses avec intervalle d'un ou plusieurs mois. D'autres collègues essayeront certainement d'autres possibilités.

Nous sommes arrivés très loin, pour revenir en arrière et désespérer; il faut continuer, persévérer, améliorer; le moment, si jamais il arrive, où l'on pourra dire que l'on peut sauver une bonne partie des cas graves de la tuberculose, comme d'autres moments semblables qu'on a déjà vécus, sera un moment de consolation, au milieu du désarroi politique, du chaos et des entretueries de notre époque.

Prof. Jose Martino da Rocha, Rio de Janeiro, Brazil.

Lantern slides were demonstrated to illustrate a technic of obtaining a series of planographic exposures of a limited part of the lung field, all recorded on a single 30 x 40 cm chest film. When the area under investigation is circumscribed and is carefully located, it is possible in this way to explore it in tomographic plane sections only a few millimeters apart and thus to obtain the maximum of information with reasonable economy of film. The method is of particular value in visualizing apical cavities.

Perdicologos and Dr. Barbara Samaras
Dr. Spiros Characopoulos, Greek Red Cross, Athens, Greece.

For routine vaccination with BCG the authors prefer Rosenthal's method of multiple scarification. Observations begun in 1944 have multiplied rapidly, so that a total of 1698 vaccinations and 774 re-vaccinations are available for analysis. Scarification requires only a modest quantity of vaccine, produces a positive skin test in 96.6 per cent of subjects, and has given rise to no severe local lesion or suppuration of regional lymph nodes. In a group of children who were given BCG by mouth as controls, a positive skin test was obtained in only 53.8 per cent.

P. W. Bræstrup, M.D. Chief of Pediatric Dept. County Hospital, Copenhagen: *B. C. G. Vaccination in Denmark.*

As a supplement to the data given by Prof. Wallgren on B. C. G. vaccination in Scandinavia, it might be of interest to mention how the vaccination is handled in Denmark, where it is probably used more than in any other country.

The subcutaneous injection of 0.1 cc of the vaccine after test with Mantoux 1/10 and 1 mg is always used. No reactions or inconveniences are seen.

The aim is to have the whole population vaccinated. First, all persons with known tuberculosis contact and nurses and medical students were vaccinated. Next, throughout vaccination of the small island Bornholm where it was proved that the normal peak of the incidents curved in late adolescence was flattened out.

Now all tuberculin negative school children are vaccinated usually at 14—15 yrs. of age.

Recently, the whole population between 16 and 35 yrs. in the city of Copenhagen, inhabiting over one million were called in for X-ray and tuberculin tests. 80 % of them turned out and the negative were vaccinated upon.

At present, Danish Red Cross supported by experts and the State Government, has the very simple and timid program to vaccinate the whole population of the European Continent. Danish State serum Institute can produce vaccine for thirty million people a year, and a team of one doctor and two nurses can examine and vaccinate from 1 200 to 2 000 people every day, starting with school boys and going on with any group they can find in factories, unions, etc.

Danish teams are now working in Poland, Hungary, Austria, and Germany, having for instance handled all school children in Warsaw. If the program can be made rolling like a snowball, it is within possibility to have at least the most susceptible age groups vaccinated upon within a few years.

ing the allergy with the B. C. G., which, for the difference of doses, the difference of way of inoculation, and difference of activity (as alive bacilli easily perishable are in question) gives different tissular reaction. With our vaccination with killed bacilli which has to be preferred to alive ones even if attenuated, a vaccinal tubercular focus is created. This focus which gives the allergy, will substitute the primary lesion and will give a favorable reactive behaviour to subsequent infections by t. b. The development of such subsequent infections has to be similar to the reinfections occurring in subjects already sensitized to t. b. The over 5 000 vaccinated in the first days of life, have lived always in the same hygienic conditions of their parents. The mortality of those vaccinated has been less than in those not vaccinated. 36 of them, controlled by us, have been exposed to open tuberculosis. Among them there were three dead: 2 for tuberculosis of whom one after complicated pertussis; a third for myopathy. The others 33 (89 %), comprising those who have demonstrated specific tubercular lesions by X-ray, are living, and in good conditions of health. Such facts of «nearly experimental certitude of resistence» are showing us that the evolution of tubercular focus, artificially created by killed bacilli, and subsequent allergy, are giving an undiscussable resistence, as we can see confronting the mortality we have in infants not vaccinated and living in contact with open forms of tuberculosis.

Dr. **Camille Kereszturi Cayley**, New York: *Comments on BCG Vaccine.*

Twenty years passed since the late Dr. William Hallock Park and I introduced the Calmette vaccine to the U. S. A.

By May 1935 there were 690 vaccinated and 755 control cases all hailing from tuberculous families in New York City carefully followed and analyzed. This ten years' study represented about \$100 000 worth of human effort.

In October 1936 we stated in the American Review of Tuberculosis:

1. «The BCG Vaccine is harmless to animals and to human beings.»
2. «The parenteral method is more effective than the oral one. By using the injection method the tuberculosis death rate can be reduced to its fourth.»
3. «The use of the BCG Vaccine should be encouraged as a public health measure in those who have not yet become infected and who later be exposed to tuberculosis in their own families.»

Unfortunately Dr. Park died at this time, the health regime changed in New York City and \$100 000 worth of research material was thrown out of the window. I went to private practice and refused to participate in the heated arguments about the value of the Calmette vaccine.

Meanwhile ten more years passed and the BCG Vaccine came back again to America. The United States Public Health Service brought it back.

May I make just one plea? The BCG work still has to be done in a well-controlled manner. This is necessary because so many emotions were stirred up about BCG during the past 20 years that one mishap with BCG which might not be a defect of the method itself may cause so much sentiment against it again that it might be discredited for another one or two decades.

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Plenary Session—Incompatibility of Blood.

RELATOR.

Erythroblastosis and the Rh Factor.

By Prof. G. de Toni.

Children's Clinic, University of Genoa, Italy.

The term erythroblastosis originally meant the pathologic finding of extra-medullary hematopoiesis. Subsequently, this term has been extended to indicate certain clinical pictures characterized by the presence of nucleated red cells in the blood.

In the newborn, it is difficult to judge what is normal physiological erythroblastemia and what is decisively abnormal. It has been almost universally accepted that as many as 5 000 normoblasts per cubic millimeter are not to be considered abnormal. This figure is not applicable to premature infants, infants, in whom higher figures may be found. These immature red cells disappear usually by the second day and very rarely are present at the end of the first week. Nucleated red cells, younger than normoblasts, are always to be considered pathologic at birth.

When these values are surpassed we can speak of fetoneonatal erythroblastosis. Following the classification of Diamond, Blackfan and Baty (1932) the three diseases hydrops fetalis, icterus gravis neonatorum and idiopathic anemia of the newborn are included in the group of feto-neonatal erythroblastosis. To these three well known diseases a new one has recently been added by Henderson in 1942, namely hepatic cirrhosis in macerated fetuses. These diseases, although apparently different, are included in the same group for the following reasons:

1) *Familial occurrence.*

The first born are usually not affected.

- 2) *Frequent alternation of each disease in children of the same parents and even in twins.*
- 3) *The possibility of the simultaneous presence of the above mentioned diseases in the same patient.*

There is insufficient time for a complete historical description of *hydrops fetalis universalis*. Suffice it to say that at first this disease was always considered to be fatal. However, Shapiro and Cohen (1939) and Salomonsen (1944) each refer to a case ending in recovery. This disease is therefore not only of obstetrical but also of pediatric interest. On its clinical side we have to remark:

- 1) Erythroblastosis is almost always present.
- 2) There is not infrequently the simultaneous presence of immature granulocytes.
- 3) Anemia is frequent, but may be completely absent. Red cell counts may be inexact in consequence of the hydremia.
- 4) Hyperhemolysis may coexist, but more often is not present.
- 5) Edema is a result of conspicuous hypoproteinemia (without excluding the possible coexisting action of disturbances of carbohydrate metabolism, exemplified by the frequency of glycogenosis).
- 6) In case of survival, edema disappears after the first week of life, together with an elevation of oncotic blood pressure (Salomonsen).

Knowledge of *icterus gravis neonatorum* is more recent than that of *hydrops universalis*. Here again time does not permit a proper recognition of all the workers in many countries who have contributed to our understanding of this disease. To single out a few for special mention would be to slight others. We do now possess a very precise picture, both clinical and pathological, of *icterus gravis*. Its main characteristics are:

- 1) Severe jaundice, present at birth, or occurring not later than the 2nd or 3rd day, which rapidly increases in intensity. In case of survival, jaundice may last some weeks, sometimes even two months.

- 2) A severe course. Death occurs in 4/5 of the cases within the first 4 or 5 days as a result of sudden nervous involvement (drowsiness, apathy, anorexia, convulsions, changes in the respiratory rhythm). Symptoms of diathesis hemorrhagica may occur.
- 3) Enlargement of the liver and spleen.
- 4) Increased bilirubin content of the blood, with a positive direct and indirect van den Bergh test, choluria and well colored stools.
- 5) Very frequent hyperchromic, macrocytic anemia with erythroblastemia.

At post-mortem examination, more or less widespread centers of extra-medullary erythropoiesis, hemosiderosis, and degeneration of the liver cells are almost constantly found. We must also mention the fact that in icterus gravis as in hydrops fetoplacentaris, glycogen storage has been described. The close relation of this disease with erythroblastosis has been proved also by Wenig (1941) and by an accurate study of Bulgarelli and Rossi (1947) in my clinic. Concerning the liver, we must also mention the masses of bile which may plug the canaliculi. In some cases this would presumably lead to organization of the thrombi and to fibrosis of intra- and extra-hepatic ducts. This occurrence may change the clinical picture of icterus gravis so that, as a consequence of the obstruction of the biliary ducts, the stools may persistently remain acholic and simulate the jaundice of biliary obstruction. Recent evidence of this possibility, such as the results of the observations of Lightwood (1943), Skelton and Tovey (1945) and Sansone (1947) of my clinic lead to a revision of the current and predominant ideas on the relations between congenital obliteration of the bile ducts and icterus gravis neonatorum.

Of great interest are the changes in the brain observed in the course of icterus gravis, namely the well known nuclear jaundice. This name is rather inadequate, for though the imbibition of the bile in the nuclear masses of the brain is conspicuous, the existence of widespread degenerative lesions in the brain cannot be denied. Wiener and Brody therefore prefer to speak of the encephalopathy

of erythroblastosis. The cause of this peculiar staining of the nuclear mass is unknown. It does not exist in any other form of jaundice (Zimmerman and Yannet).

In my clinic we are now working on bio-chemical and patho-anatomic researches which may throw some light on the obscure problem of nuclear jaundice. Dr. Bori, in preliminary studies, has shown that in the nuclear masses of the foetus or of the newborn (during the first week of life) one finds a greater quantity of vitamin C than is found in other parts of the brain. Our researches endeavour now to establish the possible relationship between this local accumulation of ascorbic acid and the elective deposit of biliary pigments. Sequelae of this encephalopathy have come to be of great importance in pediatrics from a social point of view. Undoubtedly many cases of spastic paralysis, Little's disease, and congenital choreo-athetosis are the result of it. In my clinic Sansone has collected 25 cases of extrapyramidal syndromes consequent to icterus gravis. On the other hand, we must admit the occurrence of an erythroblastic encephalopathy without nuclear jaundice and therefore with psychic sequelae only. The possibility of feeble-mindedness as a sequela is supported by the evidence of Yannet (1944), Snyder and co-workers (1945) and Sansone (1946) in my clinic.

The third disease, *idiopathic anemia of the newborn*, is not so well distinguished nosographically from the other two. It is characterized by:

- 1) Acute onset in the neonatal period, by the 7th or 8th day on the average, but sometimes later.
- 2) Tendency to spontaneous recovery even without treatment in 4/5ths of the cases, and notwithstanding the high degree of anemia (even below one million red cells).
- 3) Absence of icterus gravis, though a few cases follow a prolonged physiologic jaundice.
- 4) Inconstant erythroblastemia and extra-medullary erythropoiesis (absent in the so-called Süssstrunk type).
- 5) Moderate or absent enlargement of the liver and spleen.

The fourth erythroblastic disease is *hepatic cirrhosis in macerated fetuses*, by which Henderson meant a syndrome characterized by advanced maceration, cirrhosis, enlargement of the spleen and a large and pale placenta. This seems to be the most severe form of all the erythroblastic diseases.

Recent immunological researches have now made it clear that the erythroblastosis in all these diseases is a secondary phenomenon. Formerly there was such argument as to whether it was primary or secondary. Additional proof against the idea that it is primary is presented by Tolentino and Astaldi (1946) in my clinic. They have demonstrated that the erythroblasts in cases of fetoneonatal erythroblastosis mature *in vitro* with curves similar to those of normal erythroblasts; slight variations seem to correspond to the severity of the disease.

Darrow (1938) postulated the existence in newborn erythroblastosis of a maternal isoimmunization mechanism towards some antigens present only in the fetal red cells and absent in those of the mother. Antigens formed in the mother's organism would pass first through the placenta and afterwards through the colostrum, and would act with an antigen-antibody mechanism.

It must be acknowledged that only by the researches of Levine and Stetson (1939) and Landsteiner and Wiener (1940) do we enter a new stage of the etiopathogenetic study of newborn erythroblastic disease. Levine and Stetson, moving from a famous clinical observation, spoke of a transplacental isoimmunization and stated that the mother was immunized by a special factor, absent in her own blood, but present in the husband and the foetus who inherited it from his father. The identification of this factor (Rh) done by Landsteiner and Wiener and the numerous researches by Levine, Wiener and co-workers as well as by Witebski, Stratton, Langley, Boorman, Dodd, Mollison, Diamond, Race, Fisher, Potter and several others, allow us to increase our knowledge on the foetal and neonatal erythroblastosis. It is not feasible for me to give here even a summary of all these studies which enabled the erection of a truly great scientific construction. I would like, however, to point out that the quite different termi-

nology proposed by various authors seems to create some confusion. It would rather be preferable to adopt everywhere the same classification of Rh groups and sub-groups. I believe on my part that the one proposed by Wiener has proved rather combersome and I agree with Levine in the suggestion that the classification of the English authors be taken as a standard everywhere.

The amount of progress done in the field during the last few years, although great, has left still many obscure points which many authors (Wiener in particular) have been trying to enlighten. We think it is worthwhile to discuss now briefly the main objections that can be made against Levine's theory on the etiopathogenesis of erythroblastosis.

1) *Why does there not exist any correlation between severity of disease and titer of antibodies?*

This lack of correlation has been explained by Wiener and by Race and also Diamond as being the result of the production by the mother of a second type of antibody against the Rh factor, which has been called a blocking antibody, or an incomplete or hyper-immune antibody. This antibody has the property of in some way uniting with the red cell without causing agglutination, and yet preventing agglutination by known antiserum. This antibody may be detected by its capacity to convert known positive cells as it were into cells that seem to be Rh negative, as well as by the slide test of Diamond and Abelson, the conglutination test of Wiener, and by the use of Coombs's anti-human globulin. According to Wiener, Pedersen's X-Protein is necessary for agglutination to occur when the antibody is of the so-called blocking type.

Very recent experiments published in Italy by Lattes (1947), however, seem to diminish the importance of the conglutination test. According to the author this test performed with red cells suspended in human indifferent serum at 56° C (which therefore causes rouleaux formation) would result at least in most cases in a »pseudo-agglutination». Even if a true agglutination existed, it would be disguised, and could not therefore be useful. This reaction »cannot therefore have our unconditioned confidences».

2) *Since the disease is due to maternal antibodies, how can the symptoms in nearly all cases manifest themselves and progress after birth?*

By the previously mentioned theory of two different kinds of antibodies, Wiener tries to avoid this objection. He suggests that X protein, which is necessary for the reaction in the presence of incomplete antibodies, is not sufficiently developed in the fetus but that shortly after birth, following the marked physiological and biochemical changes of the new-born, it takes origin from the plasma components. I do not believe that this theory could explain this side of the disease, which is perhaps the most obscure of all. The objections which can be put forward to this theory are as follows:

1) Though this theory explains the later appearance of the types due to incomplete antibodies, it does not explain how things develop when the disease is caused by complete antibodies (agglutinins in icterus gravis).

2) Since «glutinins cannot bring about the clumping of the red cells without the aid of X protein», how is it then possible, at least in some few cases, that the amount of glutinin derived from the mother is so great that «the breakdown of fetal cells occurs even without the aid of X protein»?

3) Since the agglutinins, to which is closely connected the genesis of icterus gravis, do not act during pregnancy but during delivery, it should always be possible to save the child by a Caesarian section. This does not seem to occur in practice.

4) Since the disease begins during delivery, it is difficult to explain the constant enlargement of the liver and spleen at birth such as we have in icterus gravis.

I want to say a few words about an interesting though unproved hypothesis, expressed by Zironi (1946). He believes that antibodies and other substances, which check the action of them, very often coexist in the same subject. Both may be transmitted through the placenta. Were the hindering substances rapidly eliminated, only the antibodies would remain active, and one could

explain the sudden onset of antibody activity in this way. This hypothesis should be investigated further. More recently Bessis has reported the hypothesis of Holt and v. d. Branke. They agree that the normal antihemolytic power of blood plasma is greatly lowered during the course of icterus gravis neonatorum and generally in all the newborn.

3) *How can we admit that antibodies leak through the placenta?*

It does not seem possible that fetal red cells may pass through the normal placenta into maternal circulating blood. According to Javert, this may happen if placental lesions are present. Potter and Wilson describe in some women the presence of placental anomalies which permit the leakage of fetal erythrocytes. This would explain the infrequency of the disease. Because erythroblastic disease is rare in the first pregnancy, Wiener feels that leakage of red cells into the maternal circulation is not likely during pregnancy, but on the contrary, happens chiefly during delivery. In support of this theory is the fact that in subjects already sensitized, the antibody titer seldom varies during pregnancy, but does rise from the seventh to the tenth day after delivery.

Käser, thinking that the fetal and maternal blood systems constitute two completely closed systems, and that during delivery detachment of cotyledons may occur only exceptionally, does not think the hypothesis worth supporting that maternal immunization may occur from the beginning by the leakage of fetal erythrocytes. He then tried to prove the presence of the Rh factor in the placenta, and was successful in a case of icterus gravis, but was unsuccessful in the case of two Rh positive children who were healthy. He believes that the placenta represents the sensitizing organ. Concerning actual placental lesions, however, no specific changes could be found by Repetti (1946) in three cases. Bessis (1946) remarks that, in spite of their great importance, histological and histopathological placental lesions have not yet been sufficiently studied. He could not find lesions similar to those of Javert, though he admits they may have been present and afterwards got repaired.

4) *Why do only a small number of Rh negative women become immunized?*

Wiener hypothetically assumed that the capacity of the mother to become sensitized is bound to a particular property which he indicated by the letter K, which would be transmitted according to Mendelian laws by two allelomorphic genes. From statistical studies it is claimed that 97 % of subjects do not bear these properties and belong to the kk genotype. The 3 % belong to the Kk genotype; only a few subjects (0.02 %) would be homozygous for the K gene. Thus, while in a few cases the disease occurs during a first pregnancy, in other cases it occurs only after ten or even more pregnancies. Cappell (1946) for instance reports on 37 multiparous Rh negative mothers who have not lost even one child from erythroblastic disease. Since the constitutional K factor appears to be genetically determined, the Rh negative sister of a woman who has delivered an erythroblastic child is much more disposed to become sensitized than another Rh negative woman without such a familial history.

But in determining maternal sensitization, there are many other causes such as the number of pregnancies, the group and type of blood, previous blood transfusions and probably the state of nutrition, intercurrent infections and perhaps unknown hormonal factors.

5) *How is it that the A and B properties, which are far better antigens than the Rh factor, only exceptionally cause the disease?*

Levine has asserted that the red cells are protected by the simultaneous absorption of agglutinins by A and B substances present in the tissues and fluids of certain babies (secretors). Non-secretors, then, who have the A and B substance in the red cells only would be susceptible to the disease. But we must say that, according to this theory, sensitization to the A and B antigens ought to be more frequent since as many as 20 % of all persons are non-secretors. Also, against this theory stand: 1) the observation of Boorman and Dodd according to which in the non-secretors, in whom A and B properties are lacking in the saliva, sperm and other secretions, these antigens could be detected in the tissues by

means of alcoholic extraction. 2) The Rh factor is not confined exclusively to the red cells, as Levine and others thought, but is present in all tissues.

It may be, however, that the antigens of the secretions are more powerful than those of the tissues in protecting the red cells against hemolysis (Potter).

6) *Why does not a sensitized mother always have erythroblastic children?*

Dockeray and Sachs observed that mothers whose sera contained a high titer of agglutinins might deliver health babies. They thought that the antibodies could not pass through the placental barrier except under particular conditions varying in the course of pregnancy. Similar observations were reported by Goldbloom and Lubinski. As it is reported by Tzank and Dessis, some authors suggest the existence of a hormone which makes the placenta more permeable and influences leakage of antibodies.

All these opinions indeed seem rather insufficient to explain the above mentioned difficulties.

Wiener has recently proposed a new classification of diseases due to maternal-iso-immunization.

He recognizes the existence of *icterus gravis* in connection with the milking of agglutinins into the fetal circulation during labor and with the consequent formation of agglutination thrombi in capillaries and venules of organs where the circulation is slow. In this way (the mechanism is not clearly explained) erythroblastemia occurs in the marrow, whereas jaundice is due to liver damage, and nuclear jaundice is an in vivo staining reaction of dead or dying ganglion cells. Other more infrequent instances may result from univalent antibodies or from A, B or Hr sensitization.

There is a second form of congenital hemolytic disease, correlated with the presence of univalent Rh antibodies (Rh blockers or glutinins). When a higher titer of antibodies is present in the maternal serum, *hydrops fetalis* occurs; a lower titer, instead, causes a mild anemia, which usually improves by proper transfusion therapy with Rh negative blood. Nuclear jaundice does not occur in this type.

The last variety is the so-called *icterus precox*. This is a mild

disease, caused by alpha and beta antibodies, or the Hr factor, and is often confused with physiologic icterus.

If these ingenious but audacious theories should be confirmed, we shall have a useful clinical guide. As regards our own experience, we have insufficient data to support Wiener's ideas. In this opinion, we agree with Bessis (France) and Wallerstein (U. S. A.) who are not yet convinced of their truth.

Treatment.

Before the discovery of the Rh factor, transfusions and supportive therapy were employed. Now, Rh negative blood is used. The experiments of Mollison have shown that Rh negative cells survive a great deal longer in the blood stream of babies with erythroblastosis than Rh positive cells. There are, however, a few individuals who still advocate Rh positive blood.

Recently Wallerstein (1946) and Wiener have performed a new procedure in the most serious cases, consisting in a complete exchange transfusion. The results seem to be very satisfactory. When no Rh negative blood is available, the mother's washed red cells may be used. When the disease is due to A—B antigens, Wiener suggests the addition of Witebsky A and B substance to the washed red cells of the mother.

Some authors have proposed an early induction of labor, or Caesarian section in the hope of reducing the action of the antibodies. Whilst in some cases the results were good, in others the disease developed just the same, and caused the death of the baby.

Omission of breast feeding has been advised, because the antibodies might gain entrance to the infant's blood by this route. Before such a measure becomes general, it would be wise to ascertain whether the danger attributed to breast feeding be real or only theoretical. In our children who have been excluded from maternal nursing, hemolysis has been just as severe. In Italy, Monaldi-De Sanctis had the impression that when maternal nursing was continued, no particular danger occurred. Anyhow, it would be necessary that further researches demonstrate that the antibodies pass through the intestinal tract barrier without losing their specific agglutinating properties.

Prophylaxis.

Remedies given to the mother during pregnancy have not proved of value. The value of liver extract and of luteinizing hormone, advocated by some, lacks confirmation. Broman's attempt to block the reticulo-endothelial system by injecting the mother with her husband's blood was a failure. Wiener has suggested the use of typhoid and whooping cough vaccine with the idea that these antigens would compete with the Rh antigen, and thereby suppress anti-Rh antibody formation. Immunologists, however, say that the principle of the competition of antigens is not reliable. A case studied by Malaguzzi-Valeri (1946) was the significance of a genuine experiment on this subject. A primipara who had never had any blood transfusions developed typhoid fever in the fifth or sixth month of pregnancy. After birth, the infant showed early jaundice, and died on the eighth day. Clinically, the picture was characteristic of icterus gravis, and post-mortem examination confirmed this diagnosis.

Besides Wiener's method for the suppression of antibody formation, we should mention that of Homburger. He used sodium salicylate for this purpose.

As regards the infant, it is necessary to know those signs which permit recognition of the type of disease, so that adequate treatment can be instituted. The main points, recently emphasized by Wallerstein (1946), are the following:

- 1) A history of repeated stillbirths or miscarriages in the latter half of pregnancy.
- 2) A history of transfusion of the mother with Rh positive blood.
- 3) Increase in maternal icterus index and blood uric acid.
- 4) Demonstration of edema of the fetal scalp or a Buddhalike attitude of the fetus by roentgenographic study and the occurrence of excessive enlargement of the uterus.

During delivery or immediately thereafter, the following signs may suggest the possibility of erythroblastosis; icteric amniotic fluid, excessively large and pale placenta and increased numbers of nucleated red cells in the cord blood.

In this synthetic though incomplete review, we must acknowledge that in the story of erythroblastosis much has been realized and very brilliant results still continue to be achieved. We can at present affirm by means of experimental data and clinical observations, in which workers of all countries and branches of medicine have collaborated that we have acquired elements of extraordinary interest in the explanation of the etiopathogenic problem.

Nevertheless, many points are still to be explained, and numerous and sharp objections can be made to the hypotheses and theories expressed above.

In conclusion, two problems amongst others appear of capital importance for pediatricians: the treatment of the child and the prophylaxis of the mother.

Co-RELATOR.

Incompatibility of Blood.

By **Birger Broman**, M. D.¹

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Modern knowledge and research concerning the incompatibility of blood are based on certain fundamental theories and discoveries. These are, principally, the discovery of the Rh factor by Landsteiner and Wiener in 1940, and the theory put forward by Levine and Stetson in 1939 regarding the formation of an irregular agglutinin by a pregnant woman through iso-immunization from her own foetus. This theory has been extended by Levine and his co-workers in 1940—41, and now comprises certain diseases of the foetus and the newborn. With such works and theories as a starting-point, not only Levine and Wiener themselves, but also the English school with Fisher, Race, Taylor and Mourant have been in the forefront of the advances in this field.

Technical equipment and refinements of method have been the essential factors for work in this branch of research, and it is no

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more chance that up to now, with few exceptions — for instance Diamond — the leading men are serologists who have command of the intricate serological methods necessary.

In the few minutes which are available to me, it is impossible to give a survey of the present position of research concerning the incompatibility of blood. I will restrict my report to the incompatibility of blood between the mother and her foetus.

The term *heterospecific pregnancy* is used when the blood of a foetus has a blood group antigen lacking in the mother. This occurs, for instance, when the foetus belongs to group A or B, and the mother to group O, or the foetus is Rh-positive and the mother Rh-negative.

The term *incompatibility of blood in pregnancy* is used to indicate that the blood of the mother contains an antibody which *in vitro* is incompatible with an agglutinin or blood group antigen of her own foetus. In the proper sense, incompatibility of blood in pregnancy means that the blood of the mother contains an antibody which is incompatible, not only *in vitro*, but also *in vivo*, with an agglutinin in her own foetus. That is to say, in this restricted sense, such an incompatibility is always followed by an impairment of the foetus or the newborn. I shall, therefore, use the term «incompatibility of blood» in this restricted sense (Fig. no. 1).

	Bloodgroup	
	Mother	Foetus
Heterospecific pregnancy.		
The blood of the foetus has a bloodgroup antigen which its mother lacks.	O $\alpha+\beta$ A β B α Rh(-)	A or B B or AB A or AB Rh(+)
Incompatibility of blood in pregnancy.		
a) in a wider sense.	O $\alpha+\beta$	A or B
The blood of the mother contains an antibody which <i>in vitro</i> is incompatible with a bloodgroup antigen of her own foetus.	A β B α Rh(-) anti-Rh	B or AB A or AB Rh(+)
b) in the restricted sense.		
= above but with injury to the foetus.		

Fig. 1.

From the literature of the last few years, I have picked out a few points to obtain a view of the present status of the incompatibility of blood in pregnancy, and will compare it in a few items with my own experiences.

The most common incompatibility of blood in pregnancy—and that which has been the subject of most study—is the Rh incompatibility, and I shall begin with this.

With regard to the pathogenesis of the damage to the child due to Rh incompatibility (Fig. no. 2) the figure illustrates a few fundamental rules, most of which are commonly accepted as certain. Discussion about details is still in progress.

Rh incompatibility in pregnancy. Pathogenesis of impairment of foetus.

(According to Hill & Haberman, I. Lab. & Clin. Med. 31:1053:1946.)

1. The Rh antigen in the foetal erythrocytes inherited from the father.
 2. gains access to the mother's circulation
 3. evoking a maternal response of Rh-antibodies
 4. which, in turn, pass across the placenta into the foetal circulation or, after birth, are absorbed from the mother's milk and
 5. are adsorbed upon the infant's red cells
 6. resulting in their destruction to produce anaemia and jaundice or foetal hydrops.
-

Fig. 2.

At present, I wish to concentrate only on the first part of point 4, and to say a few words concerning the passage of Rh antibodies through the placenta to the foetus.

There are, as known, at least two different varieties of Rh antibodies—the agglutinin first discovered, and the so-called incomplete antibody or glutinin (Fig. no. 3 and 4). Wiener is of the opinion that, since the «glutinins» are presumably comprised of smaller molecules than agglutinins, they more readily traverse the placenta into the foetal circulation during pregnancy and are adsorbed to the surface of the foetal erythrocytes. Wiener himself says that this hypothesis is difficult to verify in cases of erythroblastosis due to Rh sensitization, since any Rh antibody passing into the foetal circulation would immediately be adsorbed

 Different methods of detecting Rh antibodies.

A. Direct methods.	Positive	Detects Rh-antibody
Serum tested against Rh-positive cells:		
1) suspended in saline	clumping	agglutinin
2) suspended in serum or plasma (<i>Wiener</i>)	clumping	'conglutinin'
3) suspended in albumin (20-30%) (<i>Diamond</i>)	clumping	'conglutinin'
B. Indirect methods.		
Serum incubated with Rh-positive cells:		
4) the cells are afterwards tested with a known serum containing a potent anti-Rh agglutinin. (<i>Race-Wiener's</i> blocking test)	no clumping	'blockers'
5) the cells are after washing tested with human antiglobulin serum. (<i>Coomb's</i> test)	clumping	'developing'

Fig. 3.

We do not, at present, know how many varieties of Rh antibodies exist.
The existence of at least two has to be proved.

According to *Wiener* there are only two kinds of Rh-antibodies:

- 1) the agglutinin or bivalent antibodies and
- 2) the incomplete agglutinin or univalent antibodies.

That is to say, conglutinis, blockers and developing antibodies are one and the same Rh-antibody.

According to *Levine* and *Hill & Haberman* it is probable that there are more than two kinds of Rh-antibodies.

That is to say, the incomplete agglutinin can be divided into different kinds. This assumption is based on certain results in the different tests for Rh sensitization.

Fig. 4.

by the Rh-positive cells of the infant and would not, therefore, be demonstrable in the serum of the infant, except where excessive amounts (more than sufficient to coat all the erythrocytes) have been acquired from the mother. *Levine*, on the other hand, finds that, in the absence of physico-chemical measurements, there is no proof that the blocking antibody is of smaller molecular size.

I have had the opportunity of investigating the case of a

woman who, from a previous pregnancy with an Rh-positive foetus, had residual Rh antibodies in high titre when she gave birth to a second child who was Rh-negative (Fig. no. 5). This child was quite healthy. The titration of the mother's blood serum and the serum from the cord blood is shown in the following table (Fig. no. 6).

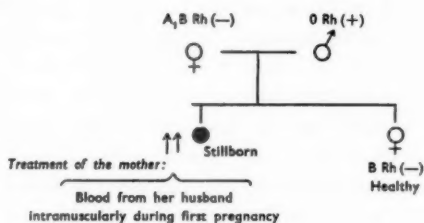


Fig. 5.

Agglutination and Conglutination Tests on Maternal and Infant Serums on the day of Birth. Previously Rh-immunized Mother, Rh-negative Infant.

		Test cells	Undil.	1:2	1:4	1:8	1:16	1:32	1:64	1:128	1:256	1:512
Mother	group A ₁ B Rh(-) Rh-antibodies from a previous pregnancy	Agglutination	OR ₂ r	+++	+++	+++	+++	++(+)	++	++	(+)	-
			OR'r	+++	+++	+++	+++	++(+)	+	(+)	-	-
Infant	group B Rh(-) cord blood	Agglutination	OR ₂ r	-	-	-	-					
			OR'r	-	-	-	-					
		Conglutination	OR ₂ r	+++	+++	+++	+++	+++	+++	++(+)	++(+)	-
			OR'r	+++	+++	+++	+++	+++	++	+	-	-

Fig. 6.

From this it is obvious that, in this case, the passage of the antibodies through the placenta occurred in accordance with Wiener's theory. The agglutinins were held back by the placenta, but the glutinins or «blockers» passed quite readily.¹

¹ Inserted in proof: Similar cases were studied by Wiener-Berlin and by Levine-Scudder, oral communications from Wiener and Levine.

With regard to the prognosis for future pregnancies in cases where a child has suffered injury on account of Rh-immunization of the mother, I have assembled a few points which are generally accepted.

The outlook for future children to an Rh-immunized woman depends, among other things, on the father's Rh genotype. Another baby might be Rh-negative with no danger of trouble, but even if the baby is Rh-positive, it may survive with treatment. According to Wiener, if a man is homozygous for the Rh factor ($R_1 R_1$ or $R_1 R_2$) and his wife's serum contains Rh blocking antibodies, every infant must be Rh-positive and the prognosis for future pregnancies is thus virtually hopeless.

In an Editorial note on the Rh factor in the last Year Book of Obstetrics and Gynaecology, Greenhill from Chicago says: «If a woman once has a baby with erythroblastosis, all babies born subsequently who are Rh-positive will have erythroblastosis. Therefore, if the husband of a woman who has given birth to an erythroblastotic baby is homozygous, all the future babies will be Rh-positive and will have erythroblastosis.»

It is understandable if the theories thus put forward regarding the prognosis for further pregnancies give the non-expert the impression that, after Rh-typing of the husband of an Rh-immunized woman, it is possible to make a definite prognosis in this respect. But with the present more generally accessible Rh-typing anti-serums (anti-Rh', anti-Rh°, anti-Rh'' and anti-Hr', or — according to British nomenclature — anti-C, anti-D, anti-E and anti-c) it is, however, not always possible to judge the genotype particularly with regard to the homozygote Rh-positive bloods (Fig. no. 7 and 8). Thus, for example, a father whom we from our typing results presume belongs to the genotype $R_1 R_1$ or $R_1 R_2$ can, as we are aware, belong to the type $R'R_1$ or $R'R_2$ respectively. If an Rh-immunized wife of such a man only shows Rh antibodies of the type anti-Rh° (anti-D), but not of anti-Rh' (anti-C), it is possible for her, with such a «homozygote» Rh-positive husband, to give birth to a healthy child of the type $R'r$. I have seen such a case, and the following slide (Fig. no. 9) will show the most important data. I feel that we ought to assess,

Rh Nomenclature.

Agglutinins		Genes	
Wiener	Fisher-Race	Wiener	Fisher-Race
anti-Rh'	anti-C	R ^o	cDe
anti-Rh ₀	anti-D	R'	Cde
anti-Rh''	anti-E	R''	cdE
anti-Hr'	anti-e	R ^{o'} (R ₁)	CDe
(anti-Hr ₀)	(anti-d Diamond)	R ^{o''} (R ₂)	cDE
(anti-Hr'')	(anti-e Mourant)	R ^{o'''} (R ₂)	CDE
		R''' (R _y)	CdE
		r	cde

Fig. 7.

Rh Nomenclature.

Reactions of 927 Bloods with four anti-Rh typing Serums (Fisher & Race).

Rh'	Anti-		Hr'	Most frequent genotype in group	per cent
C	Rh ₀ D	Rh'' E	c		
-	+	+	+	R ₂ r	12.19
+	+	+	+	R ₁ R ₂	13.59
+	+	-	+	R ₁ r	35.17
-	-	-	+	r r	14.78
+	+	-	-	R ₁ R ₁	19.74
-	-	+	+	R'' r	1.29
-	+	-	+	R ₀ r	2.48
+	-	-	+	R' r	0.65
+	+	+	-	R ₁ R _s	0.11
+	-	+	+	R' R''	-
+	-	-	-	R' R'	-
+	-	+	-	(R _y) R'	-

Fig. 8.

with caution, the prognosis for future children even when the husband after typing is thought to be homozygote Rh-positive.

The importance of the AB0 system in the occurrence of injuries to the foetus appears to be extremely difficult to assess. According to the AB0 system, as many as approximately 25 % of all pregnancies are heterospecific (i. e., the mother belongs to group 0 and the child to A or B; or the mother to B and the child

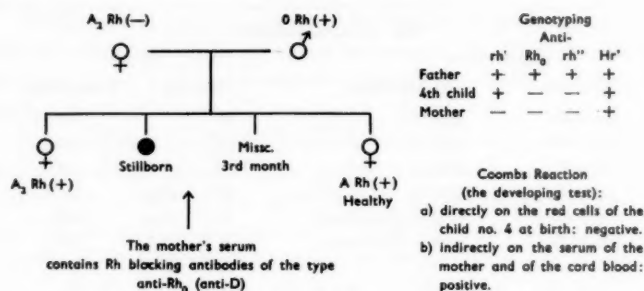


Fig. 9.

to A or AB; or the mother to A and the child to B or AB). That such heterospecific pregnancies often give rise to an iso-immunization of the mother against the A or B antigens of the child appears to be established since Jonsson in Sweden in 1936 was able to demonstrate a specific increase of the isolysin frequency in such mothers. More recently, other workers, such as Smith in England in 1945, have been able to demonstrate that an increase in the iso-agglutinin titre is also present in such cases. In spite, however, of the immunization of the mother, both these writers, as well as many others, found only healthy children in their series.

In other words, incompatibility in the widest meaning of the term according to the ABO system, with incompatibility of the mother's serum in vitro with the red cells of the child, although it often results in an iso-immunization of the mother, does not as a rule cause injury to the foetus. These circumstances are thus in direct opposition to the findings according to the Rh system.

Thus in the ABO system, there is not as a rule — despite the occurrence of iso-immunization — any incompatibility of blood in the strict meaning of the term. Nevertheless, a few isolated cases can occur in which we have reason to assume ABO immunization as a pathogenic factor in a haemolytic disease of the newborn. Race in 1945 was, however, of the opinion that only one convincing case had hitherto been published, namely one reported by Aubert, Cochrane and Ellis in the same year. These authors

reported a case of hydrops foetalis, where the serum of the mother contained phenomenally large amounts of anti-A (titre 1/16 million) and — which is considered particularly significant by Race — although the infant belonged to group A, it had strong anti-A in its serum. From a purely statistical point of view, however, Halbrecht in 1944 and Wiener in 1946 are of the opinion that they have received support for their assumption of a not altogether uncommon, but most frequently insignificant effect on the foetus (so-called icterus neonatorum praecox) in heterospecific pregnancies according to the AB0 system and, in individual cases, according to Wiener, injuries of the type erythroblastosis foetalis sometimes occur.

In individual cases, Wiener endeavours to verify his pathogenic viewpoint by the examination of anti-A and anti-B titres in the mother's serum. He has thereby found, at times, that the conglutinin titre is considerably higher than the agglutinin titre in these cases, and considers that this constitutes proof of the presence of other antibodies than the natural agglutinins formed in the mother, which antibodies are injurious to the foetus.

However, I do not personally know of any case of haemolytic disease which is considered to be caused by immunization in the AB0 system, where a positive Coombs reaction was obtained directly on the red cells of the child. At present, however, the general opinion appears to be that the antibodies in the AB0 system are not of such a character that they can give a positive Coombs reaction. Nevertheless, in the autumn of 1946, Boorman and Dodd in England gave a preliminary report concerning an incomplete form of anti-A agglutinin, and stated that a positive Coombs reaction could be obtained in the AB0 system. The question of the relation of Coombs reaction to the AB0 system appears, therefore, at present to be uncertain.

The fact that, in direct testing of the red cells of the newborn by Coombs reaction in suspected haemolytic disease due to anti-A or anti-B immunization, a negative result is obtained, cannot thus — contrary to the circumstances in Rh incompatibility — be given decisive importance. We are, therefore, in individual cases, most often extremely uncertain as to the significance of the AB0

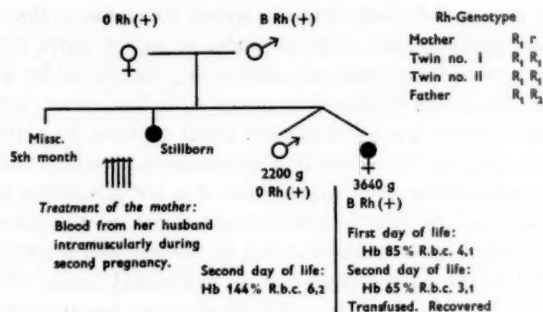


Fig. 10.

system in a possible disease in the newborn child. In most cases it is, therefore, often a question of presumptive proof.

I have myself seen a case of anaemia in one of newborn twins, where there was reason to suspect B-immunization of the mother as the cause (Fig. no. 10).

Other blood-group systems than the two just mentioned (the Rh and the AB0), very seldom appear to be the cause of injury to the foetus or the newborn infant due to immunization of the mother. No case has been published within the MN or P system. However, another antigen, «Kell», which does not appear to be connected with any of the known blood groups, has probably been responsible for a case of haemolytic disease of the newborn, according to papers by Coombs, Mourant & Race (1945, 1946). The mother, who was «Kell» negative, had in her serum an antibody which agglutinated the cells of her children, her husband and about 7 % of random bloods. The cells of the infant were shown by the Coombs test to have been sensitized in utero. The baby was severely anaemic, but not jaundiced, and it responded satisfactorily to a blood transfusion.

We are aware that the typical familial erythroblastotic disease in its different manifestations (foetal hydrops, anaemia or icterus gravis) is the injury inflicted on the foetus or the newborn infant on account of incompatibility with regard to the Rh system, when the mother is Rh-negative and the child is Rh-positive. All cases

Survey of the distribution of Rh groups in different materials of erythroblastosis foetalis.

	Total	Number Mother Rh(+)	% Rh(+) of total
Levine et al. [†] (1942)	350	35	10
Boorman et al. (1942)	48	2	4
Potter et al. (1943)	60	6	10
Brewer (1943)	5	0	—
Wiener (1943)	43	6	14
Race et al. (1943)	50	6	12
Broman (1944)	42	6	14
Gammelgaard (1945)	17	4	23
	615	65	11 %

Fig. 11.

of erythroblastosis cannot, however, be explained on the grounds of such incompatibility, since approximately 10 % of children suffering from this disease have Rh-positive mothers (Fig. no. 11).

It is possible that, in these series, in which the cases have usually been collected from a number of different quarters, there must be a great risk that cases of disease outside the bounds of true erythroblastotic affections are included in them. In order to determine this, the material can be divided into two groups. Group I includes such erythroblastotic cases where, besides the course of the disease in the child, the family history is typical — that is to say that at least the first-born child was healthy at birth and at least one child besides the one in question must have contracted erythroblastosis. All the remaining cases come under Group II.

A division like this, where the cases have to conform to fairly rigid requirements before they are assigned to Group I, means that Group II will also contain quite a number of cases doubtlessly belonging to the true erythroblastotic diseases. The reason is, of course, the requirements as to familial occurrence, whereby a child with only one older brother or sister can never be referred to Group I. Moreover, the requirement that the first-born must be healthy, means that all erythroblastotic children in families where the first-born suffered from any illness will not be assigned to Group I.

Race, Taylor et al. 50, Broman 42, Gammelgaard 17 (Total 109).

	Total	Number Mother Rh(+)	% Rh(+) of total
<i>Erythroblastosis foetalis</i>	109	16	14
Typical familial ¹	36	1	2.8
The rest	73	15	20.5

¹ At least the first-born child healthy at birth and in addition at least two children which have contracted erythroblastosis.

Fig. 12.

Unfortunately, data concerning family histories is lacking in the majority of the publications, and therefore only 3 series, from England, Sweden and Denmark, comprising in all 109 cases can be treated in this way (Fig. no. 12).

In such a classification we see that the frequency of Rh-positive mothers decreases considerably in that part of the material where only definite cases of familial erythroblastotic disease are included. In other words, we can estimate that, of the approximately 10 % of Rh-positive mothers with erythroblastotic children, only 2—3 % have had children who in reality suffered from familial erythroblastosis. Of this 2—3 % with Rh-positive mothers, a number of cases must be caused by more uncommon Rh-immunizations (with the occurrence of anti-rh'' and anti-Hr' — or anti-E and anti-c) a number by the blood group antigens of which we have no detailed knowledge (e. g., the so-called «Kell» antigen) and, finally, only an extremely small number caused by incompatibility according to the ABO system. In my opinion, recent publications appear to exaggerate the importance of the ABO system in this respect.

The question of the aetiology of the remaining 7—8 % of the cases of foetal erythroblastosis of non-typical familial character must, for the present, remain open. It appears very probable that, in these cases, incompatibility of blood has had no pathogenic significance.

I wish to say only a few words concerning the therapy of infants affected by Rh-immunization. In the state of present knowledge, the most important measures consist of immediate supply

of warmth, fluids and oxygen, as well as transfusion, preferably into the cord, of blood belonging to the same Rh group as the mother, but free from Rh antibodies. Despite such treatment, far from all children with erythroblastosis are saved, but the mortality of live-born children with this disease has, nevertheless, considerably decreased — from about 75 % to approximately 20—30 %. Thus there is still a great need for improved therapy, and numerous suggestions have been put forward. Of these, two in particular have aroused general interest, namely, artificially induced labour or caesarian section before term, and exchange blood transfusion of the newborn.

Several authors have suggested artificially induced labor or caesarian section before term in an Rh-immunized woman. It has also been suggested that the mother's blood in such a case should be closely watched for the appearance of antibodies, and that pregnancy be terminated at the time when such antibodies show an excessive rise or sudden fall, and the foetus is viable. Diamond goes so far as to state in 1945 that «this is one of the two methods of proved value in assisting the previously sensitized Rh-negative mother to have a living Rh-positive infant». He reports that, in 41 cases of early induction of labour on account of a rising anti-Rh agglutinin, there have been 32 living and 9 dead children, that is, a primary mortality of over 20 %.

Other writers, for example King and Burch, are dubious about the value of such intervention and yet others, such as Greenhill, at present advise against such a measure.

It appears possible that recent publications, which aim at correlating the degree of severity of the infant's illness with the time of appearance of the antibodies during pregnancy or the antibody titre will afford us a basis for deciding which cases are suitable for artificially induced labor or caesarian section before term. However, the majority of experiences hitherto with this method have been very disappointing. In my opinion, we cannot expect that only an early artificially induced labor in selected cases will give noteworthy results, even when Hill and Habermans, and Page Hunt and Lucia's works have been definitely verified, and their experiences concerning the correlation between the developing

titre or the time of appearance of the Rh antibodies during pregnancy and the injury to the child have been applied in practice.

Regarding exchange transfusion during the first hours of life, which appears to be carried out — where the method is applied — on almost all Rh-positive children of Rh-immunized mothers, such an intervention would perhaps seem too great, since it is somewhat problematical whether it would produce a more satisfactory effect than an ordinary transfusion. This method should be attempted on a series of children where the mother has already had two or more still-births. In such cases, a combination of caesarian section before term and an exchange transfusion would appear a possible solution. Saving severe cases of this kind is the true criteria for a satisfactory method of treating erythroblastosis. We hope that the results of the series of early termination of pregnancy and exchange transfusion which have been carried out will be published at the earliest possible opportunity, together with complete family histories in addition to the serological findings. In this way we will have greater possibilities than at present for assessing the value of these methods.

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CO-RELATOR.

**The Pathogenesis of the Hemolytic Diseases of the Newborn
with Special Reference to the A and B Antigens
(Icterus Praecox).**

By **I. Halbrecht, M. D.**

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Thanks to the fundamental studies of Levine and Wiener, the major part of the explanation for the pathogenesis of erythroblastosis foetalis that still was mystifying not so long ago, was found and substantiated. Nevertheless, many paradoxical problems connected with the hemolytic diseases of the newborn remain unsolved. We want to mention just a few of them:

(1) The term 'hemolytic diseases of the newborn' that was given to this group of clinical symptoms and that comprises the hydrops congenita, the icterus gravis and the anemia congenita is based upon the, thus far, undisputed finding that hemolysis is the primary and most important symptom of this syndrome. However, this is true only as far as the anemia congenita (which is the least severe form and the rarest condition of this syndrome) is concerned. On the other hand, the most severe forms of the icterus gravis show only a mild anemia or none at all. In some cases of icterus gravis we found, shortly before the death of the infant, as many as 7 000 000 erythrocytes per cmm. The erythroblastic infants surely did not die of anemia, but in a shock-like toxic state. Hence, there is an etiologic connection between the intensity of hemolytic processes in the blood of the newborn and the gravity of the clinical symptoms but far out of proportion. This leads us to the assumption that there exists, in addition to the hemolysis, a particular (perhaps allergic) sensitivity in the newborn which causes most alarming clinical symptoms in spite of a less severe hemolysis. This sensitivity (should future research prove it to be a reality) is perhaps caused by a hereditary constitutional factor. The following observation may serve to strengthen our hypothesis: We had occasion to observe two Rh-negative sisters who were married to two Rh-positive men. Both

women were delivered of erythroblastic babies only — altogether 4 — and none survived.

(2) Not every Rh-negative mother is being iso-immunized by her Rh-positive baby. The ratio of the number of definitely iso-immunized mothers to the number of possible iso-immunizations is 1:25. This phenomenon, too, may be explained eventually by a special susceptibility to immunization caused by a constitutional hereditary factor (Wiener's 'K' factor). (1)

It is difficult to explain the disproportion between the titer of the antibodies in the blood of the mother and the intensity of hemolytic symptoms in the infant. Moreover, the cases reported in which anti-Rh agglutinins occur in the maternal blood without any hemolytic symptoms in the infant are becoming more numerous. (2)

(3) Another paradox that, up to now, has not been explained convincingly is the fact that the α , β -agglutinins, which are, contrary to the Rh agglutinins, natural antibodies, only rarely cause erythroblastosis in heterospecific pregnancies but produce, most frequently, only light hemolytic symptoms in the newborn. The only plausible explanation of this phenomenon is the binding of the α , β -agglutinins of the mother by the A and B antigens that occur in the tissues and body fluids. These antigens occur in a water-soluble and fat-soluble form in the secretors, but only in a fat-soluble form in the nonsecretors.

Only in the red cells was the Rh factor proved to occur definitively. Some authors are of the opinion that it can be found in cells of other organs also. (3) This difference in the occurrence of the antigens should explain the different reactions of the newborn to the anti-Rh and the α , β -agglutinins of the mother.

We found A and B antigens in the erythrocytes of the fetus at a very early stage. (4) In two cases we found A and B agglutinogens in fetu not older than ten weeks. This disproves the assertion that the A and B antigens develop in the fetus later than the Rh factor. Neither could we substantiate Wiener's hypothesis (5) that the placenta is more easily penetrated by the Rh blocking antibodies (glutinins) than by the α , β -agglutinins.

We examined the umbilical blood of 200 newly born babies

and we found agglutinins in 38 per cent of all cases. Contrary to most investigators we could prove that at least one part of the agglutinins is being produced in the blood of the newborn itself, agglutinating the erythrocytes of the mother. (6) On the other hand, there can be no doubt that the α , β -agglutinins found in the umbilical blood are derived from the maternal blood, for after a short period of time they disappear completely from the blood of the newborn. Undoubtedly in cases of heterospecific pregnancies the α , β -agglutinins of the mother may produce hemolytic symptoms in the newborn. Rarely, however, do they show one of the forms of erythroblastosis foetalis.

In most cases the antigen-antibody reaction in heterospecific pregnancies appears to have a much milder form. We called it 'icterus praecox'. (7)

Icterus praecox.

This form of jaundice in the newborn is distinguished by two characteristics: (1) the early appearance of the icterus during the first twenty-four hours after birth, and (2) the intensity of the jaundice, which may, and frequently does, cause a mistaken diagnosis of icterus gravis. In addition to these two characteristics the icterus praecox differs from the icterus gravis in the following points: (a) The infant having icterus praecox does not show any toxic symptoms. (b) The blood shows no anomalies except an elevated bilirubin concentration (0.75—2.8 milligrams per hundred cubic centimeters), no erythroblasts (or only a few), no anemia (or only a mild form). In most cases there were over 5 000 000 red cells per cc; in some cases the number drops to 4 500 000, and only in rare cases did we find anemias of 3 500 000. (c) The icterus praecox appears more frequently than the erythroblastosis foetalis in the *first* offspring. (d) The prognosis of icterus praecox always is favorable and even those cases with 3 500 000 red cells needed no blood transfusion.

In 95 per cent of all cases we deal with a heterospecific pregnancy in which the red cells of the baby were agglutinated by the agglutinins in the maternal blood. In most cases the mother belonged to type 0 and the baby to type A or B.

The icterus praecox occurs in about 1:120 newborn. Since heterospecific pregnancies constitute approximately 25 per cent of all pregnancies, it follows that the icterus praecox occurs only in about 1:25 heterospecific pregnancies. This fact is the more remarkable since the erythroblastosis foetalis, which is caused by the Rh factor, appears in the same proportion to the combination of Rh-negative mothers and Rh-positive fathers. It is possible, therefore, that the same constitutional hereditary factor that is responsible for the occurrence of erythroblastosis foetalis by means of the Rh factor, favors also the appearance of icterus praecox in heterospecific pregnancies.

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Discussion.

Dr. Bruce Chown, Winnipeg, Canada:

All three speakers have raised questions to which we can give no answer. All have questioned the complete validity of Levine's original hypothesis. Dr. Broman's last slides showed that 7 to 8 per cent of cases of non-familial erythroblastosis foetalis are apparently not due to an antigen-antibody reaction. If, on further investigation, this statement proves unquestionably true (and Levine has made a similar one) it raises the question whether *any* cases of erythroblastosis foetalis are due *solely* to an antigen-antibody reaction. Please mark the word 'solely'.

Levine's hypothesis has been of enormous help. It covers much and yet it does not cover all. Consider these facts:

1. Of the four major syndromes of erythroblastosis foetalis at least three, namely congenital anaemia, severe jaundice, and hydrops foetalis, can occur apart from presently demonstrable blood incompatibility, and in the absence of syphilis, sepsis and maternal diabetes. Potter particularly has reported on cases of hydrops.
2. Hydrops with erythroblastosis and without blood incompatibility may occur in first pregnancies.

3. When hydrops occurs in the foetus gross oedema is likely to occur in the mother.
4. Out of 125 families that I have investigated in the past two years, in which erythroblastosis is believed to have occurred, or in which the mothers had antibodies but bore normal babies, there were 8 families in which one or more *apparently* normal Rh-positive children were born subsequent to the birth of one or more *apparently* erythroblastotic children. This suggests that the disease producing mechanism can be spontaneously suppressed.
5. Anti-Rh antibodies may disappear from a woman's blood while she is carrying a normal Rh-positive foetus.
6. As Dr. Halbrecht has pointed out, in icterus gravis the probability of death is almost inversely proportional to the degree of anaemia developing after birth.
7. Histopathologically some cases of certain erythroblastosis show practically no evidence of extramedullary erythropoiesis; most have a very small thymus; many have adrenal lesions; some have one or more of the following: — basophilia of the pituitary, hyperplasia of the islets of Langerhans, hypercalcification of the long bones, enlargement of the heart.
8. Apart from transfusion the following methods of treatment have been reported to be successful.
 - (a) Estrogens with maternal urine (de Snoo).
 - (b) Maternal serum (Hampson).

Time permitting, one might cite other evidence. I ask you but to consider this: granting the antigen-antibody reaction, granting the haemolysis, then, in most cases, there is a successful reaction to that haemolysis. Severe anaemia at birth is rare. Some counterbalancing mechanism is called into play that, up to birth, results in adequate replacement of the destroyed blood. What is that mechanism? What governs it? Why does it fail after birth? We do not know. It is probably humoral. May it not be that, as a side effect, that mechanism itself produces much of the picture we call erythroblastosis foetalis; that, by itself, apart from blood incompatibility, it produces the non-familial examples of the disease; that, by its failure or exhaustion, it leads to such things as death in icterus gravis? Professor De Toni has said the two most important practical matters are treatment of the baby and prophylaxis of the mother. Prophylaxis of the mother will only come from a search for this countervailing mechanism. Serology will tell us why haemolysis occurs. It will be metabolic and physiologic studies that will tell us why haemolysis is overcome, or disease suppressed, and teach us how we may imitate Nature.

Dr. Louis K. Diamond, Boston:

An analysis of over 3 000 war veterans, who have received one or more transfusions while in the service, revealed that the expected percentage of Rh negative recipients is found. Of these, the expected statistical number probably received Rh positive blood. Fifty-three per cent of the Rh negative recipients reveal antibodies against the Rh blood type when proper analysis of their serum is carried out. Such analysis is made not only by the saline agglutination method, but also by suspension of red cells in albumin, in albumin and plasma mixtures, and by the quick screening slide test developed in our laboratory. The Coombs test (rabbit anti-human globulin) confirmed the presence of the incomplete (English terminology) or hyper-immune antibody, but does not reveal any sensitization missed by the albumin testing method.

An analysis of a limited number of women who received Rh positive blood injections or blood transfusions, followed by pregnancy, reveals an even higher incidence of Rh antibodies, about 80 per cent. The number of cases tested is too small for a true statistical evaluation, but there seems to be no doubt that even intramuscular injection and certainly intravenous blood injection of incompatible type in women, with the possibility of increasing or resensitizing these subjects by subsequent pregnancies is much more likely to produce Rh and other antibodies than any other method so far found.

Finally, a small number of children found to have received blood incompatible according to Rh typing has been followed in this clinic and here too about fifty per cent of the patients show Rh antibodies by the several different methods of testing.

A brief review of the testing methods and the results found in these various groups of patients is offered in this paper. (Illustrations by lantern slides.)

Leonard G. Parsons, M. D., F. R. C. P., and H. S. Baar, M. D. (From the Department of Paediatrics, University of Birmingham, England.)

Despite the great advances which have been made in the knowledge of haemolytic disease of the newborn in recent years, the problems concerned with the production, prevention and treatment of nuclear jaundice still await complete solution. For instance is kernicterus due to excessive haemolysis or to vascular obstruction such as occurs in liver necroses produced experimentally by the use of immune sera, or is it the direct result of antibody fixation in the nerve cells or a sequence of hepatic disease and only indirectly due to Rh antibodies. In this communication we propose briefly to record the results of our investigations and thereby to give what we believe to be the answers to some of these questions and to show that with the resources at present at our disposal, prevention and cure are alike impossible.

1. No relationship has ever been found between the degree of haemolysis and the degree of icterus nor between the degree of haemolysis and the presence of kernicterus. Severe icterus has occurred with evidence of the Rh immunization of the mother but without any signs of abnormal haemolysis in the baby, and conversely severe haemolysis has occurred in the baby, accompanied by only a slight trace of jaundice and without the production of kernicterus.

2. Haemolytic-hypoplastic anaemia produced by damage to the blood forming organs by antibody fixation in the tissues has persisted for many months, thus indicating that the antibody acts on the whole erythron and not on the red cell only.

3. Damage to the liver has always been present in icterus gravis as shown by: Dissociation of liver cell trabeculae; the presence of swollen cells packed with pigment granules or droplets; necrosis or necrobiosis, and also in some instances abnormal cholesterol partition, a biphasic van den Bergh reaction, impairment of sugar tolerance and the late development of cirrhosis of the liver.

4. The basal ganglia have been found to be bile stained in icterus gravis within 18 hours of birth indicating that changes in the brain probably occurred before birth. Other evidence supporting this suggestion is: The occurrence of the disease in macerated and hydropic fetuses and also in premature and still-born babies; the presence of hydrops or jaundice at birth; the development of jaundice shortly after birth.

5. The histological changes observed in the brain can be classified under three heads: (a) proliferative (b) inflammatory and proliferative (c) degenerative necrobiotic and necrotic.

(a) *The proliferative changes* consisted in the appearance of layers of undifferentiated glia cells in the deeper parts of the subependyma.

(b) *The inflammatory and proliferative changes* were manifested both as perivascular crescents in the neighbourhood of the cerebral ventricles, resembling those seen in Virchow's encephalitis interstitialis neonatorum, and also as perivascular cuffs similar to those occurring in epidemic encephalitis; in addition there was also a cellular infiltration of the sub-arachnoid space.

The changes described under heads (a) and (b) were found in icterus gravis both with and without kernicterus, in haemolytic anaemia of the newborn, and in certain other diseases of the neonatal period particularly sepsis neonatorum.

(c) *Degenerative necrobiotic and necrotic changes.* The nerve cells of the basal ganglia showed either chromatolysis with nuclear pyknosis or a 'fading away' first of the nucleus with the production of ghost cells and then of the whole cell. The great variability in the individual cells was most striking, normal cells being in close proximity to cells which were completely necrosed. Bilirubin was present in the cytoplasm of the nerve

cells showing chromatolysis and also in some but not in all the ghost cells; it was apparently of the normal type and repeatedly showed a change of colour to green. In addition to the necrosis of individual nerve cells there were microscopical foci of necrosis. These foci were associated with round cell infiltration and were not limited to the central gray matter but were occasionally observed in the white matter and still more rarely in the cerebral cortex. The result of all these changes was the replacement of nerve cells by an astrocytic gliosis. Severe changes were only met with in kernicterus but milder changes were seen in hydrops foetalis and in haemolytic anaemia of the newborn. With occasional exceptions compound granule cells were usually scanty or absent in kernicterus thus contrasting with the findings in other necrotic diseases of the brain.

6. Typical macroscopic and microscopic areas of kernicterus were observed in two children who died from neonatal sepsis. Isoimmunization was excluded in these children by serological investigations which included not only Rh antibodies but also natural agglutinins and pan-, or anti O-agglutinins.

7. Similar microscopic appearances to these seen in kernicterus but without any bile staining were found in the brain of an unjaundiced child who died 24 hours after birth and in whose liver haemorrhagic miliary necroses were found.

8. Complete Rh antibodies were found in babies with hydrops foetalis and haemolytic anaemia of the newborn and occasionally only blocking antibodies were found in the sera of mothers who gave birth to an infant with icterus gravis.

The absence of necrotic changes and of bile staining of the brain in hydrops is probably due to the excretion of bile and toxic products via the placenta and not, as suggested by Wiener, to a different pathogenesis. As a matter of fact the development of jaundice and the occurrence of kernicterus had been recorded in a child suffering from extreme anaemia and mild hydrops who survived for two days (Cappell). This placental excretion is also according to Cappell the probable reason why many children who suffer from icterus gravis do not show jaundice at birth. This suggestion seems to us to receive great support from the fact that children with congenital obliteration of the bile ducts do not develop jaundice until a short time after birth.

Our conception of what happens in kernicterus is as follows: Rh antibodies are fixed in the liver cells (Boorman & Dodd) and the damage thus produced renders the liver incapable of dealing with the toxic products of metabolism; as a result, a hepatogenic encephalopathy arises comparable with that occurring in lenticular degeneration and in the Eck fistula of experimental animals, the bile staining being secondary to the necrotic and necrobiotic changes. The view that staining is secondary to injury of

the brain cells is supported by recent experimental work (Day); one hemisphere of the brain in rats was stained yellow when, after damaging the area with X-rays, the rats were rendered icteric by tying the common bile duct and by intravenous injections of bilirubin.

We do not know why kernicterus is limited to the neonatal period. It is not due to protection by the myelin sheaths since the localization of the changes shows no relation to the degree of myelination. The immaturity and/or the large water content of the brain of the newborn baby may be connected with its particular susceptibility to hepatic encephalopathy and bile-staining since there appears to be a greater proportion of immature and weak infants amongst those who die from kernicterus. We have seen nuclear jaundice in twins on two and in triplets on one occasion.

If our explanation of the origin of kernicterus is correct the possibility of protecting the liver by intravenous injections of glucose, the administration of insulin, calcium gluconate, liver extract, methionin and cholin should be considered. Transfusions of Rh negative blood only relieve the anaemia and do not affect the incidence of kernicterus. We fail to see how exsanguination transfusion or indeed the protective treatment of the liver can affect changes which have occurred before and even after birth unless the antigen-antibody reaction is reversible; so far there is not any convincing evidence that this reaction is reversible.

Prof. Aldo Muggia, Quito, Ecuador: *The Rh Factor and the hemotherapy in the Vomiting of Pregnancy.*

The most recent factor, the Rh antigen (agglutinin) was described by Landsteiner and Wiener (1940—1941): these authors observed that injecting erythrocytes of *Macacus Rhesus* to a rabbit or guinea pig would cause the serum of these animals to agglutinate the cells of 85 % of the white persons in America and would not agglutinate the other 15 %: these two classes are called Rh positive and Rh negative. A similar distribution, with marked racial differences, has also been found in other parts, for example in Great Britain (Boorman, Dodd and Molli-son — 1942, Hoare — 1943, Taylor and Race — 1944). In the American negro population the number of the positives is greater: in some races the Rh-negatives are very rare: Landsteiner, Wiener and Matson found only one in 120 American Indians and one in 150 Chinese. Rh is inherited as a dominant characteristic, its presence being determined by the gene Rh and its absence by the gene rh: it is present at Birth. Perhaps the most important discovery of these past years concerning human heredity has been the identification in genetics of the different blood groups: our present age has contributed proofs of great originality of thought and methods and it is difficult to establish limits to the possibilities which the geneticist, embryologist, and physiologist can give rise to. The groups A, B, and O are inherited according to Mendelian principles

as was shown by Berstein: the child receives from each parent one of the three antigen A, B, or O. No child can have an antigen which was not present in one of the parents. The serum of certain persons who had hemolytic reactions after blood transfusions compatible according to the system A, B, and O contained agglutinins identical with the anti-Rh factor. All the receptors were Rh negative or had received transfusions previously or concerned pregnant women. The first group was immunized by repeated transfusions of positive blood. The second, by the Rh antigen present in the fetus, inherited from the father and passing through the placenta from the fetus to the mother. The relationship between the mother's immunity and the hemolytic illness of the newborn is the result of the immunization of the mother by an erythrocyte antigen which the child has inherited from the father followed by the passage of the antibody through the placenta with the result that it acts in the fetal blood. As 90 % of the mothers in question are Rh negative, the anti-Rh factor can be found in the serum of a great proportion of them, and as every child from such a mother who has been examined always resulted as Rh positives, there can be no doubt of the importance of the Rh factor as the cause of this illness.

In 10 % of the cases in which the mother is Rh positive it seems that there should exist another erythrocyte antigen which is responsible: only anti-A and anti-B are found regularly in human serum under normal conditions. The antibodies of group alfa, and anti-O are found now and then, and anti-M is very rare. Any of the above antigens or some unknown one could give rise to an immunization, causing a reaction in the transfusion or the hemolytic illness in the newborn. The recessive rh gene produces an antigen and the agglutinins which arise with it have been produced by mothers who are lacking in them by children who have erythroblastosis and have received rh from their parents and it is possible that some of the cases with Rh positives mothers are caused by this type of agglutinins.

The first or the first two sons in a family are hardly ever affected by hemolytic illness caused by the Rh factor: Levine showed that when the first son was affected the mother ordinarily has a past history of blood transfusions and fail to mention that the same effects can be produced by hemotherapy. In my opinion, this treatment causes the same dangers as blood transfusions. I was able to observe two cases of erythroblastosis which have been recognized as having this origin and which have been reported by Gmo. Rojas Sucre (Bol. de la Federación Medica del Ecuador — 1947, 111, p. 10).

Summaryzing the cases are the following.

Case I: Mrs. L. G., 38 years old, of the mestiza race, married, the husband is also mestizo and healthy.

Family History: The mother had 15 children, 3 abortionsbrothers are alive, five married and have families: all are healthy.

Personal History: common children illnesses, married at the age of 19, has had nine births and no abortions.

Obstetric History: first pregnancy — vomiting from the beginning of pregnancy and the doctor recommended hemotherapy from her husband's blood which was not carried out because of the mother-in-law who would not allow her son to be weakened. Birth was normal and the daughter lives.

Second Pregnancy — intense vomiting and hemotherapy is recommended but is not carried out. Pregnancy is normal and ends with normal birth and healthy child.

Third Pregnancy: vomiting occurs and hemotherapy is recommended but again it is not carried through. Pregnancy is normal and ends with normal birth and healthy child.

Fourth Pregnancy: vomiting is severe from the first weeks. On this occasion, the first injection of 10 cc of blood is made . . . Pregnancy is normal and ends with normal birth and healthy child.

Fifth Pregnancy: vomiting is repeated: ends with normal birth and a live child, but the child dies in two days with *ictericia*.

Sixth Pregnancy: everything is more or less alright with discrete vomiting. Birth is normal, child is alive, but also dies in two days with *ictericia*.

Seventh Pregnancy: everything goes well, birth ends with a living daughter who dies in four days with *ictericia*.

Eighth Pregnancy: vomiting from the second month. Hemotherapy is indicated and six injections from the blood of the husband are made. It ends with premature birth in eight months with the child dead in the uterus.

Ninth Pregnancy: everything goes well until the ninth month and ends with normal birth and a live child who has *ictericia* on the third day. Shortly before death (fourth day) Dr. Rojas made a hemolytic examination: fetal erythroblastosis of the *ictericia* type was observed. The mother is Rh negative with abundant quantity of agglutinins of the anti-Rh type, the child is Rh positive, same as the father.

Case II: Mrs. R. A., 30 years old, white race, has had three pregnancies.

Family History: The grandmother dies at an advanced age. The grandfather died at an accident at 70 years of age. Parents are alive and healthy. There are five brothers.

Personal History: Children's illnesses, no other illness.

Obstetric History: first pregnancy: unconstrainable vomiting from the first weeks. The doctor recommended hemotherapy with her husband's blood: Seven injections were made of 10 cc each with a 48 hour

interval between each one, vomiting disappeared as if by magic. Pregnancy ends well with normal birth and living daughter. On the third day, the daughter exhibits serious ictericia which evolves rapidly. She dies the following day. The mother observed that her milk was very yellow.

Second Pregnancy: discrete vomiting. It stopped at 8 1/2 months of pregnancy with the fetus dead and macerated.

Third Pregnancy: intense vomiting at the beginning of pregnancy. Two injections from the husband's blood are made. The married couple both showed negative serological reactions. Antisyphilitic treatment was made. Premature birth at 8 1/2 months resulted with the child dead and macerated.

Investigations in the fetus showed a fetal erythroblastosis of icteric form. The formula was: mother = Rh negative, father = Rh positive, fetus = Rh positive. The existence of anti-Rh agglutinins was found in the mother until two months after birth.

These cases show the importance which physicians must place in preventing the uncontrolled use of hemotherapy using the husband's blood in gestating mothers who have severe vomiting if there is no laboratory at hand in which hemolytic studies can be made. Once more the pathogenicity of fetal erythroblastosis and neonatal is confirmed as being found on a hemolytic process and also the ictericia of the newborn could be attributed to an accidental placental transfusion of incompatible blood.

Plenary Session.—“Alimentary Toxicosis”.

RELATOR.

Alimentary Toxicosis; Water and Mineral Exchange in Diarrhea.

By E. Kerpel-Fronius, Pécs, Hungary.

Alimentary toxicosis has been described by the past great generation of Pediatricians as a condition secondary to diarrhea, characterized by severe constitutional symptoms similar to those which accompany poisoning.

The manifestations of Toxicosis are not confined to any specific type of diarrhea, or infection. Rather they are a symptom complex representing the particular reaction of the infantile organism to various infectious agents (1).

Clinically the most prominent feature of a toxic condition is circulatory shock, accompanied by nervous symptoms and acidosis. The other well-known symptoms, described by Finkelstein (2) may sometimes be absent.

It is my endeavour in this brief account to describe the *essential steps leading from diarrhea to toxicosis*. A number of theories have been advanced to explain the causal relationship between diarrhea and toxicosis. Those relating to dehydration and toxin formation have received the most attention. I shall briefly describe the foundation and clinical justification for these theories.

Trousseau (3) impressed by the precipitous weight loss and similarity of the entire picture to cholera, recognized the importance of dehydration. The direct effect of dehydration on the brain as well as liver function was first thought to have a bearing on the origin of toxic manifestations (4, 1). For the last 25 years however, the comprehensive and simple *anhydremic* theory of Marriott (5) has become more widely accepted. The main features of the latter

being that vomiting and diarrhea cause an «anhydremic» diminution of blood volume, leading to shock and consequently to disintegration of cellular life.

The causal relationship between the loss of electrolytes and the origin of anhydremia was discovered by Gamble (6). Briefly, the loss of gastro-intestinal secretions caused by diarrhea, and containing the same structural elements as blood plasma, lead to dehydration because water can not be retained in the body without electrolytes. The final phase of dehydration is the reduction of plasma volume leading to the appearance of the so-called toxic symptoms.

This implies that in base loss the regulatory mechanism is «set» as to maintain a constant concentration of electrolytes. Therefore a loss of body water ensues, quantitatively adjusted to the extent of base loss.

In certain circumstances however, the osmotic regulating mechanism does not function satisfactorily although the tendency to maintain optimum electrolytic concentration is always present.

In this connection it is of some significance that the ability of the *infantile kidney* to maintain osmotic constancy has been found in dogs (7) and humans (8, 9) to be inferior to that of adults. Even variation in salt, protein and water intake may lead to variation in blood freezing points from -0.42° — -0.95° in puppies. The same diets do not alter the milieu interieur of adult dogs (7, 10).

It seems of importance in considering this problem to discuss some instances of defective or delayed osmotic regulation in *experimental* as well as *clinical* studies of anhydremia.

Osmotic regulation works almost perfectly in the presence of a continuous loss of *digestive secretions*. A decrease of plasma base occurs only in the terminal, anhydremic stage of dehydration.

Anhydremia may however appear, without water-loss, if a significant amount of extracellular electrolytes is suddenly withdrawn (11). Secondly an osmotic shift of water occurs from the extracellular fluid to the cells, while the body fluids remain hypotonic. Thereafter an osmotic readjustment takes place. According to Gamble's *theorie* water is lost from the body nearly proportional to the amount of sodium loss. Therefore the final picture corres-

Sodium, Water and Plasma Volume Losses in Different Types of Dehydration.

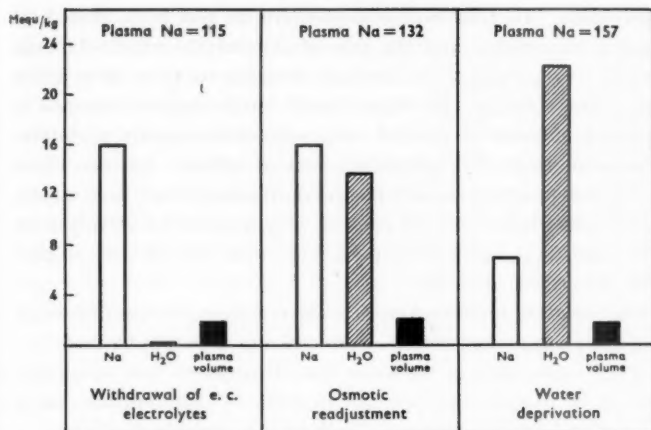


Diagram I.

ponds to that of anhydremia caused by the loss of digestive secretions: The anhydremia and sodium deficiency persist, dehydration proceeds to an extent that body fluids are again nearly isotonic.

Let us now discuss a *fundamentally different type of anhydremia*. If an animal is submitted to *total fluid deprivation*, the renal excretion of Na and Cl lags behind the water loss, and the concentration of blood sodium climbs higher and higher. This rapid rise of osmotic concentration in the extracellular fluid constantly drains water from the intracellular compartment. In sharp contrast to the preceding pictures of anhydremia, the latter is reached only after a most impressive water loss amounting to 20 % of initial body weight. The loss of base being insignificant relatively, while the body fluids remain hypertonic.

It is interesting to note that the importance of electrolyte loss in the etiology of dehydration, which is so familiar in *America*, has in the past not been fully appreciated in *Europe*. If we analyze the reasons for this, we must first recall the observations of early workers pertaining to the rôle of salt in alimentary fever (2).

Furthermore I think that in animal experimentation on toxicosis the chief method used to cause dehydration was simple water deprivation. In this »water depletion», as has been stated, the blood is hypertonic and the loss of electrolytes relatively unimportant. Consequently it seemed illogical to treat dehydration with saline solution. In some French clinics hyperchloremia and increased chloride of the red corpuscles were equally understood to contraindicate the administration of saline. Balance experiments and practical experience have demonstrated that strongly negative salt balances may coexist with increased electrolyte concentration in the case of imperfect osmotic adjustment as previously described (83—86).

On the other hand in America, the constancy of osmotic regulation, its primacy on volume preservation was emphasized.

This contradiction between the »European» and »American» concept of dehydration led me in 1935 to differentiate, on the basis of balance experiments, between the »water depletion» and »salt depletion» types (12). Recently these facts were substantiated by English and American observers (13—18).

Summing up, the relationship between anhydremia, body electrolytes, and body water, the data presented indicate clearly the need for the differentiation of the various types of dehydration with reference to their origin. On this basis, as shown in diagram I anhydremia may appear preceded either by base or water loss of variable extent, and may eventually be accompanied by hyper- or hypotonicity of the body fluids. In circumstances which endanger both, osmotic and volume constancy, the organism generally compromises and neither function is fully carried out.

Now let us analyze anhydremia in its relation to the osmotic regulating mechanism in *clinical cases* as against *experimentation*.

There certainly are some types of dehydration corresponding to the »water depletion» type just discussed. Dehydration of the *newborn* may be quoted as an example. Of peculiar interest is the exceptional form of toxicosis in which the *pneumonic loss of water* caused by hyperpnoea leads to dehydration. Vomiting and diarrhea are absent, the osmotic concentration of the blood is high, and the urine contains only traces of chloride (20—22).

Conversely, if preceded by diarrhea and vomiting, dehydration is connected necessarily with a loss of electrolytes. This was shown to be true by balance experiments both in adults and infants (23—28). As a matter of fact this was already known in the past century by the great cholera students (29—31).

The more intensive the diarrhea, the nearer the concentration of chloride in the stools approaches plasma values (32). This fact is indicative of the importance of faulty reabsorption of digestive juices (33). Indeed diarrheal dehydration corresponds to the classic «salt depletion» type as produced in the model experiments of Gamble (33). In many instances factors are operating in the manner previously described, making an ideal osmotic adjustment impossible, and the *concentration of plasma base will accordingly be normal, decreased or even increased*. The concentration of plasma chloride is even more variable inasmuch it is influenced by the degree of vomiting (33—36).

The question which now arises is whether *diarrheal anhydremia caused by the loss of extracellular electrolytes is alone the key problem of every type of toxicosis or whether there are other factors involved*.

A rough answer to this question is given in diagram II, where I have tried to show how new findings were paralleled by the mortality rate decrease from toxicosis.

I am well aware that the data used in the construction of this chart (36—45), must of necessity be carefully analyzed. The statistics on the mortality of toxicosis depend not only on therapy but also on the age, nutritional condition, character of the underlying infection, and gravity of the toxic condition (46).

It is evident from the diagram that the parenteral use of water led to a sharp drop in mortality, especially if care was taken to replace the electrolyte loss. On the other hand, no matter how ingenious was the composition of the therapeutic solution, about half the infants still died.

The *acidosis* obviously can not be held responsible for the limited efficacy of repair therapy. As a matter of fact I may quote Hartmann (36); the acidosis was corrected and the correction confirmed by analysis of the electrolyte pattern. It is puzzling that the comatose state and shock persisted even after the character-

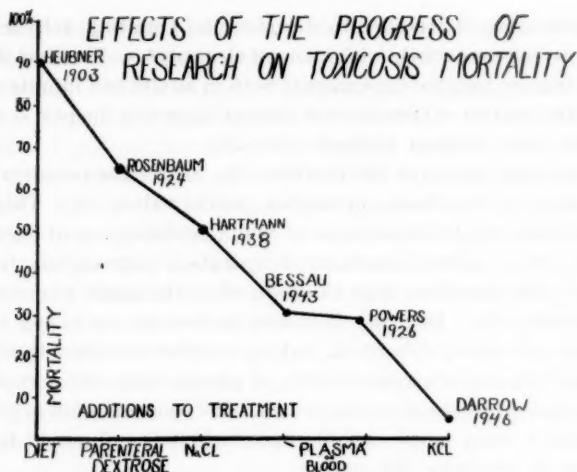


Diagram II.

istic breathing and other evidence of acidosis had disappeared (47, 36).

From the chart we observe that simple repair of dehydration and acidosis still leaves us a mortality of about 50 %. It is therefore clearly necessary to *seek other factors which may play a part in the mortality rate*. Shock is universally recognized as one of the key problems of toxicosis. In some cases there is a discrepancy between weight loss and the appearance of shock. Cases of enteral toxicosis are observed associated with minor weight losses, and detoxication may proceed with flat, or even ascending weight curves (48, 49). In some instances these anomalies can be explained by osmotic water shifts between the fluid compartments. But please, let me emphasize that we are dealing more frequently with real enteral *infections*. We all know and recognize that infectious agents play a part in the genesis of circulatory failure.

Another important factor is the discrepancy sometimes observed between the larger increase in the red count and the proportionately smaller increase in serum protein, thus permitting the eventual escape of fluid and protein from the capillary system

(50, 51). On post-mortem examination capillary dilatation with pericapillary edema and small hemorrhages are usually demonstrable in the brain, lung and skin. According to Langstein terminal pneumonia is frequently found (52). In Moon's opinion this complication is characteristic of «toxic» capillary damage (53). In toxic infants Khokhol found signs of serious capillary injury by means of a capillary microscope (54). By the method of Landis (55) increased capillary leakage can be detected (56).

Last but not least we may conclude from the diagram that the mortality statistics of Powers (45), who used early transfusions, and Bessau, (39) who used large doses of plasma, are more favorable than those where only simple solutions were given. We all know that intravenous plasma is superior to saline in the treatment of shock accompanied by vascular injury (50, 57).

In this connection it is interesting that in the invasive period of respiratory infections and diarrhea one may observe *prior* to the development of dehydration a particular type of circulatory failure first described by Kiss. The demonstrable signs and symptoms in such cases are similar to toxicosis. One notes a semicomatose condition, an increase in pulse rate up to 200, cardiac dilatation as seen by X-ray, and coronary circulation impairment as demonstrable by means of EKG. Strophanthin relieves this condition (58).

Thus the evidence is accumulating that vascular damage may be an important contributory factor in the etiology of circulatory failure in many cases of toxicosis.

The essential processes underlying the toxic syndrome are not confined, however, only to extracellular fluid and circulatory failure. The *cells* themselves are damaged by the reduction of at least one of their structural elements, namely *potassium*. The vital importance of this element has long been appreciated in general biology. Ernst in Hungary (59) was the first to demonstrate its importance in the processes involved in muscle fiber contraction. Butler and I have found in rabbits that following the repeated administration of diuretin enormous losses of sodium, chloride and potassium occurred and death ensued even when the loss of extracellular electrolytes were replaced. We felt that this was due to the marked potassium loss (60).

To Darrow and Govan must go the credit for having shown that during diarrhea the potassium loss is replaceable. Its subsequent addition to routine treatment led to an unexpected low mortality (61).

I feel that a description of toxicosis would be hopelessly incomplete without some discussion of the *neurologic symptoms*, which are among its most prominent features. Some pathologic changes in the brain have been described recently which may have a bearing on their origin. The meninges are injected, edematous, and hemorrhages are demonstrable. Vascular changes are also observed in the parenchyma itself. The dilated capillaries are encircled by edematous loosened brain substance. There are signs of degeneration, sometimes amounting to necrosis (62, 63, 83). Marquézy and Ladet, Ribedeau-Dumas pointed out the similarity of these changes to those found in death occurring in fulminating infections (64, 65). It is a great temptation to look upon these changes as part of a general capillary injury, as previously mentioned in the discussion on the etiology of shock.

This leads us to the evaluation of the rôle of poisonous substances in producing this capillary damage. The toxic products of the milk or bacterial action may be considered here. At the time when Finkelstein first used the term «Alimentary Toxicosis», he obviously thought of the former possibility (2).

Since then, an everincreasing percentage of so-called «alimentary» cases have been found to be true enteral infections. We encounter reports from Italy, Hungary, Germany, America that summer diarrheas caused by different strains of the dysentery bacillus are more frequent than would have been suspected on the basis of the clinical picture or post-mortem findings. It is important therefore to note that measures directed toward the prevention of «infectious» diarrhea led also to the decrease of «nonspecific» diarrhea (66—70). In many cases where there is no obvious exogenous infection, abnormal bacterial growth especially of colon bacilli may occur in the upper part of the intestine, a section normally sterile (71). Many authorities believe that these organisms produce either, toxic products, or that they may act in an abnormal manner on the milk protein producing toxic, histamin-like sub-

stances. Both are possible. We know that bacteria are present and that the permeability of the intestine is greater during inflammation as well as the earlier month of life. It is equally possible in young animals to produce a picture having all the essential features of toxicosis by the oral administration of histamin-like substances or filtrates of colon and dysentery bacilli or simple dehydration (71—83).

In conclusion, I think that at the risk of somewhat oversimplifying the subject, toxicosis may be understood as the picture of shock in infancy. First, the failure of circulation may be simply due to reduction of plasma volume caused by diarrheal loss of water and electrolytes. These would be «alimentary» cases, readily influenced by withholding food and replacing lost water and electrolytes. Second, in the larger group, the shock is only partially anhydremic in origin. The catabolites of infective agents are damaging to the capillaries and circulation, thus rendering the condition more refractory to simple replacement therapy. In both groups, although secondary features, vascular damage to the brain, interference with cellular life by potassium loss and shock are essential. The success of therapeutic measures elaborated in the light of theoretical knowledge lends support to the accuracy of these views.

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CO-RELATOR.

»Alimentary Toxicosis».

Por A. A. Aballí, Havana, Cuba.

En el estudio de la toxicosis del lactante, la clinica permite diferenciar primordialmente dos grandes sindromes:

- 1 — Un síndrome de insuficiencia circulatoria periferica (shock circulatorio)
- 2 — Un síndrome encefalopático (encefalopatía aguda).

Ambos pueden asociarse en el mismo enfermo en grados variables, o existir aisladamente, y en las etapas finales las manifestaciones de uno y otro pueden ser indiferenciables.

El síndrome de insuficiencia circulatoria periferica es, sin duda alguna, el mas constante, y constituye el cuadro unico o predominante en una proporción elevada de los casos observados. La deshidratación es el factor principal en la patogenia de este shock. La acidosis que usualmente acompaña a la deshidratación, también interviene en la producción del mismo.

La importancia de la toxemia bacteriana ha sido practicamente olvidada en estos ultimos tiempos. Ella, sin embargo, interviene amenudo, en mayor o menor grado, en la producción

de la misma insuficiencia circulatoria periferica. En la infeccion enteral especifica su papel resulta especialmente importante. En algunos casos se observan manifestaciones de shock antes de aparecer la diarrea, y tanto la insuficiencia circulatoria como otros trastornos dependientes de la toxemia mejoran considerablemente al iniciarse o intensificarse las mismas. Estos casos probablemente han sido los que popularizaron en otra epoca el empleo de la medicacion purgante.

La intervencion de toxinas productoras de shock, elaboradas por colibacilos o paracoli en las partes altas del intestino, carece de suficientes pruebas clinicas para su aceptacion.

La hipoglicemia es la causa del shock en una proporcion bastante elevada de los casos prolongados de toxicosis que ocurren en niños distrofosicos.

En un 14 % de nuestra casuistica hospitalaria se presentaron manifestaciones nerviosas de bastante intensidad. En algunos de los casos ocurrieron desde los inicios de la enfermedad, aun precediendo a la aparicion de los trastornos gastrointestinales.

La elevada mortalidad (mas de 60 %) de los casos con manifestaciones nerviosas nos obliga a estudiarlos con especial interes.

Las infecciones parenterales mas graves se acompañan, frecuentemente, de trastornos del sistema nervioso.

En las infecciones enterales (aun sin tener en cuenta las producidas por la *Shigella Shiga*) se observa una predisposicion mucho mayor a manifestaciones de este tipo.

La frecuente asociacion de los fenomenos nerviosos con grandes hiperpirexias, hace pensar en una posible alteracion en la distribucion de los liquidos cerebrales, como la que han demostrado experimentalmente Yanet y Darrow.

La necropsia, en algunas ocasiones, revela la presencia de trombosis de las venas cerebrales, o de los senos de la duramadre, que explican satisfactoriamente el cuadro encefalopatico, pero las mas de las veces solo demuestra la existencia de alteraciones inespecificas.

La alcalosis, la carencia de Tiamina, y la uremia, parecen explicar la sintomatologia nerviosa en algunos casos aislados.

A menudo hemos notado la aparicion de un sindrome neurologico grave despues de la rehidratacion. En la mayor parte de estos casos, las cantidades de liquidos empleadas han sido exageradas. En otros enfermos es posible que el trastorno dependiera del deficit de calcio en los liquidos extracelulares que han demostrado recientemente Rappaport y colaboradores.

Ademas de los cuadros que hemos señalado deben tomarse en consideracion las alteraciones de organos vitales que pueden ocurrir en estos procesos; entre ellas la insuficiencia hepatica, las lesiones miocardicas, las deficiencias de la funcion adrenal, y los trastornos renales son los mas importantes. Estas pueden influir en la produccion de algunos de los trastornos a que nos hemos ya referido o producir manifestaciones adicionales.

El deficit de minerales no extracelulares, en el curso de las diarreas infantiles, ha sido demostrado en los ultimos años. El papel de las deficiencias existentes en la produccion de los trastornos clinicos observados, es, en la actualidad, objeto de extensas investigaciones.

En sintesis, la intoxicacion alimenticia o toxicosis es un sindrome complejo, debido casi siempre a combinaciones variadas de alteraciones de orden toxiinfeccioso y de orden metabolico (Anhidremia — Acidosis — Deficit de otros minerales — Hipoglicemia etc.). El pretender encontrar una patogenia unica ha sido el mayor fracaso de muchos de los que hasta ahora han investigado el problema.

Existen grandes variaciones en la susceptibilidad individual del niño a la intoxicacion. En el momento actual los niños bien nutridos, pertenecientes a la clase media y acomodada, raras veces presentan esos cuadros, aun en presencia de diarreas profusas. Esto contrasta con lo que ocurre en los lactantes carenciados que acuden a nuestros hospitales de caridad. En ellos no solamente se observa una predisposicion a la deshidratacion, sino que tambien ocurren con mayor facilidad las complicaciones nerviosas.

Una serie de hechos observados en nuestro Hospital en los ultimos años puede contribuir algo a la explicacion de estas diferencias.

El hallazgo de cifras relativamente bajas de proteina, para el grado de deshidratacion existente, ha sido frecuente en los casos de rehidratacion dificil y de esclerema. (Ilustraciones.)

En ocasiones la administracion de aminoacidos no era capaz de mejorar la hipoproteinemia, por existir una insuficiencia hepatica. (Ilustracion.)

Las alteraciones de la funcion hepatica son frecuentes en estados carenciales de la infancia (pelagrosos).

La carencia de Tiamina, por si sola, es capaz de producir, en el niño pequeño, estados de acidosis intensos, que ceden a la administracion exclusiva de la vitamina. Ademas en los casos de beriberi del lactante, las manifestaciones nerviosas forman una parte prominente del cuadro. (Ilustraciones.)

Los niños mal nutridos presentan, a menudo, grandes perturbaciones del metabolismo de los hidratos de carbono, que se acentuan en el curso de las infecciones. A veces estas alteraciones dependen de una insuficiencia hepatica, pero mas frecuentemente parece existir un mecanismo de produccion mucho mas complejo. (Posiblemente una deficiencia de hormonas antagonicas a la insulina.) (Ilustraciones.)

Los niños carenciados presentan una predisposicion especial a las diarreas en el curso de infecciones parenterales.

La susceptibilidad del distrofico y del carenciado a la toxicosis, explican, al menos parcialmente, la enorme frecuencia de estos trastornos en el pasado, cuando los regimenes que se administraban al niño eran muchisimo mas restringidos que en la actualidad.

Las consideraciones anteriores nos permiten sacar en conclusion que la mayor profilaxis de la intoxicacion alimenticia o toxicosis es:

- 1ro. — La alimentacion natural adecuada.
- 2do. — La alimentacion artificial balanceada y suficiente (cuando no puede realizarse la anterior).
- 3ro. — El tratamiento precoz, satisfactorio, de las diarreas agudas, dirigido a controlar la diarrea y su causa, y a aportar o restituir aquellos elementos que, de acuerdo

con el caso, parezcan ser los que van a caer en estados de deficiencia.

En el cuidado del caso de toxicosis establecida, no solamente es necesario tener en cuenta el síndrome clínico y humoral existente, sino también debe considerarse el estado nutritivo anterior del niño, el tipo de infección concomitante, y las alteraciones viscerales que puedan estar presentes. El conocimiento de la fisiopatología de este a veces complicado proceso, es necesario para que el médico que trate esta clase de trastornos obtenga los mejores resultados.

CO-RELATOR.

Alimentary Toxicosis.

By **L. F. Meyer**, Tel-Aviv, Palestine.

Alimentary toxicosis with its triad of cardinal signs, loss of weight, coma and deep breathing is still a very frequent condition in tropical and subtropical countries, where it makes its appearance with the first khamseen (sirocco) in April and disappears in November. During the summer of 1946, 260 cases passed through my ward, with the peak of 46 cases coming in August.

The onset of toxicosis is as intimately associated with dehydration as is detoxication with the restoration of cellular fluids (*Finkelstein's law*).

The dehydration of toxicosis has an obligatory precursor phase of diarrhea and vomiting, alimentary in origin or resulting from some enteral or parenteral infection. It is not always easy to distinguish between toxicosis of an alimentary or of a specific infectious origin, typhoid, paratyphoid or dysentery.

Some dehydrating substance is apparently produced during the course of the pathological digestion of food in the gastrointestinal tract by an abnormal intestinal flora or by the usual flora invading the small intestine which is normally sterile; these substances, on entering the blood stream, bring about dehydration and the depletion of extra and intracellular fluids and minerals.

Toxicosis has always been considered one of the most serious of all diseases of infants. The fatality rate, not so many years ago, was 60—70 %.

Our therapeutic endeavours, which I intend to discuss, are aimed at two points: first, to hinder the harmful interplay between germs and foodstuffs, which is the preparatory stage for toxicosis, and, second, the battle against the dehydration and the restoration of fluids and salts to the organism. We attempted to attain the first aim by complete hunger, providing water; — several authors even maintained this hunger up to a week; — and then we started the feedings with a very gradually increasing amount of a carefully chosen diet. These attempts were frequently without success. In the fight against dehydration we gave salts and water prepared according to the tissue reactions (acidosis or alkalosis) by all routes subcutaneous, intraperitoneal, intratibial, intravenous, venoclysis for several days, etc. There may have been a slight improvement but in spite of these measures we still had a very high mortality in 1940 — 50 % — and the same held true for other institutions. So we had to resign ourselves, as did Czerny, with the words: »The dry child can be refreshed and revived with tea and water, whereas the wilted child cannot be resuscitated even by the most complex intravenous injections.»

The situation was completely altered when pediatrics was presented with the sulfa drugs. COOPER and his co-workers were, as far as could be ascertained from the literature, the first to use sulfathiazole and MARSHAL and his co-workers were the first to advocate the introduction of sulfaguanidine; but use of these sulfa drugs was restricted by these authors to specific dysenteries. Even today, January, 1947, such well known workers as WEIHL, RAPOPORT, and DODD speak only of the specific antidyenteric value of the sulfa drugs.

We have been giving these drugs to all diarrheas regardless of etiology since 1941. Sulfathiazole was the drug of choice in dyspepsias of the first half year and in all cases of toxicosis; the use of sulfaguanidine was reserved for specific enteral infections and for the non-specific diarrheas of older children.

We have recently added oral potassium chloride to our treatment, as was first suggested by DARROW, in order to combat the loss of intracellular potassium. We seem to have slightly better results since. This therapeutic routine is well known to most pediatricians; the rapidity of detoxication and the return to normal stools is associated with a marked increase in weight even while the child is on the submaintenance diet. We called these curves, resembling a V, victory curves.

NASSAU, experimenting with acacia cubes and sprouting beans, showed the positive influence of sulfathiazole on water binding in colloidal substances and living tissues; he believes sulfathiazole to act as a specific agent for the reassertion of the normal water binding powers of the tissue. The success of this treatment is proclaimed by statistics; whereas previously a 50 % fatality rate was not considered too bad, we had a fatality rate of 13 % in the first year of treatment and during the last few years it has fallen to 7 %. An improvement in life expectancy which was previously unimaginable.

The mode of action of sulfa is not easy to explain: One suggestion that may be reasonable is that its effect is primarily on the preparatory phase of toxicosis by the prevention of abnormal digestion of food and by reasserting normal fermentative digestion.

The bacteriostatic powers of the sulfa drugs combat and overcome the abnormal or abnormally situated germs of the G. I. tract as I discussed above. The pathological chain of events is thus broken at its first link and the faulty digestion of food ceases. We still have no idea as to which of all the intestinal bacteria are affected by sulfa drugs or as to whether it is a question of quantity alone.

We have not ceased our search with sulfathiazole. We have been trying the great antibiotic, penicillin, on diarrheas and toxicosis since the end of 1946 with apparent clinical success.

It is generally well established that the effect of penicillin is markedly decreased or is completely destroyed when given by the oral route. HENDERSON and ADAMS, basing themselves on the fact that the gastric acidity up to the age of 9 months is very

low, P. H. 5 as compared with P. H. 1 in adults, gave penicillin to infants by mouth and found relatively high and efficiently bacteriostatic blood levels.

We have confirmed these findings and have found relatively high blood levels in most cases 4—8 U/100 cc after giving 40 000 units per os.

It may therefore be assumed that the factors which make the oral administration of penicillin unreliable in adults are not present at this early age. On the basis of these facts, we have used oral penicillin in toxicosis and diarrhea and vomiting, with heartening results.

We have treated more than 60 cases, 20 of which were real toxicosis. Two of these patients, whose illnesses were complicated by parenteral infections, died. The number is still too small to draw definite conclusions, but I can say that the results are encouraging.

I may cautiously sum up, that there is a similar bacteriostatic effect on the flora of the intestinal tract as that of sulfathiazole; which of the bacteria are influenced we still cannot determine. We have not noticed any changes in the usual stool bacteria.

SELIGMAN and his co-workers in New York were more fortunate. They used oral streptomycin for the first time in cases of diarrhea of the new-born, which proved to be caused by salmonella. Streptomycin, contrary to penicillin, is not absorbed from the G. I. tract and only traces can be detected in the blood and urine. Most of it remains unchanged in the bowels. The effect of streptomycin was one of distinct bacteriostasis; — during and shortly after the ingestion of the drug the pathogenic as well as the normal intestinal flora were inhibited. Sterile stools resulted («Sterilisatio Magna»).

This effect was only temporary. Clinical observations have not yet come to my attention. Theoretically, the influence of oral streptomycin is of great interest not only in the fight against specific infections, but also as a treatment in cases of toxicosis and its precursors, diarrhea and vomiting. We are only at the beginning of a new chapter in treatment. Much more work will

be needed to decide, which of the germs are sensitive to the antibiotics in order to work out the indications. Our present day treatment of toxicosis is no more a complex physical dietetic one alone, but is chemotherapeutic and antibiotic as well.

We may close by pointing out that our dietetics are now much simpler and our results much better than in the past.

I wish to thank Dr. RAPAPORT, the bacteriologist of the Municipal »Hospital Hadassah» Tel-Aviv, for his friendly help.

Discussion.

Prof. G. Fanconi, Zürich, Schweiz.

Die Toxikose lässt sich am besten definieren als eine Stoffwechselkatakastrophie, die die fundamentalen Lebensfunktionen wie Gehirn- und Herztätigkeit, Kreislauf und Atmung, schwer in Mitleidenschaft zieht.

Die Aetiologie und die Pathogenese der Anfangsstadien sind ganz verschieden. Je fortgeschrittener die Störung, desto ähnlicher wird das klinische Bild, schliesslich haben wir eine völlig unspezifische Allgemeinreaktion. Wenn wir von den exogenen Noxen absehen, kann man folgende Wege erwähnen, die zur Stoffwechselkatastrophe führen:

I. Die Austrocknung, der einfache Wasserverlust (exsiccatio simplex).

Erste Stufe: Zuerst Erhöhung des osmotischen Druckes. Die Plasmamenge, welche für die Zirkulation notwendig ist, bleibt erhalten durch Abnahme vor allem der extrazellulären Flüssigkeit, aber auch infolge des Darrow-Jannel'schen Mechanismus der intrazellulären Flüssigkeit. Resultat: Hypersalämie (Pseudohyperchlorie).

Zweite Stufe: Ist der Flüssigkeitsverlust zu weit fortgeschritten, so nimmt auch die Plasmamenge ab; es kommt zur Anhydrämie. Erst jetzt wird der Zustand bedrohlich, weil Kreislauf, Hirn- und Nierenfunktion zu versagen beginnen. Wir erkennen diese zweite Stufe am Ansteigen des Plasmaeiweisses, des Hämoglobins und der Erythrozytenzahl. Diese zweite klinisch viel imposantere Stufe kann unvermittelt einsetzen.

Dritte Stufe: Die Kapillaren werden auch für Kolloide permeabel, es kommt zur serösen Entzündung, erkennbar am Sinken des Plasmaeiweisses. Klinisch ist die dritte Stufe unter anderm durch schwere Gehirnsymptome charakterisiert; autoptisch findet man ein Hirnoedem trotz der allgemeinen Austrocknung.

Status liquid extracellularis

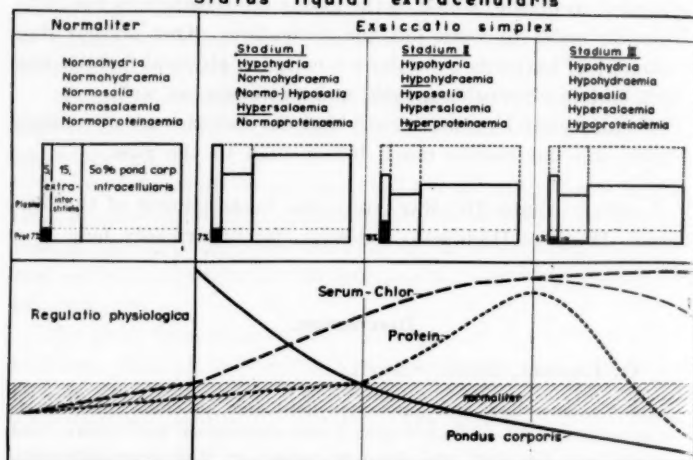


Fig. 1.

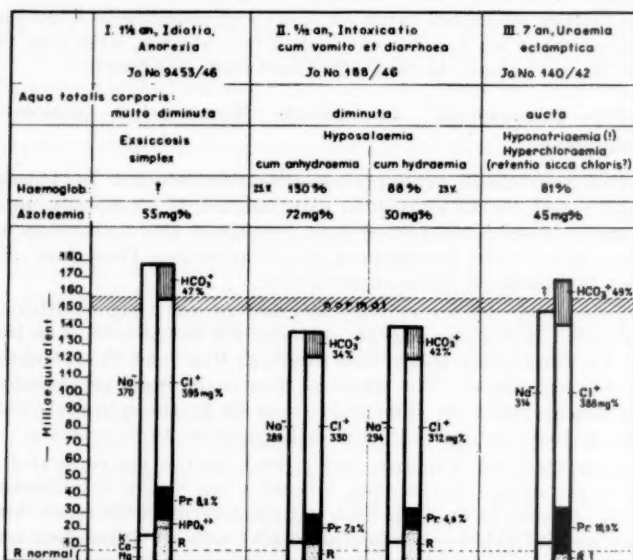


Fig. 2.

II. Verlust an Magendarmsäften, welcher zur Hyposalämie führt.

Wenn das Erbrechen vorherrscht, so kommt es zu Verlust von saurem Magensaft, d. h. von $\text{NaCl} + \text{Cl}$; herrschen Durchfälle vor, zum Verlust von alkalischem Dünndarmsaft, also von $\text{NaCl} + \text{Na}$. Der Na-Verlust führt zwangsläufig zur Hypomose, der Cl-Verlust kann durch Zunahme der Alkalireserve ausgeglichen werden. Im Gegensatz zur einfachen Exsikkose (I) sinkt der osmotische Druck auch wenn der Wasserverlust beträchtlich ist. Da Exsikkose und Hyposalämie die molare Ionenstruktur des Serums im entgegengesetzten Sinne beeinflussen, kann man gelegentlich eine scheinbar nahezu normale Ionenstruktur finden trotz schwersten klinischen Symptomen. So waren in einem Falle von schwerer Exsikkose im Praecoma diabeticum die chemischen Werte für Na (321 mg%), Cl (348 mg%) und Alkalireserve (37.5 %) nur wenig verändert, einzig das Eiweiss war auf 10.0 % angestiegen.

III. Bei akuter Niereninsuffizienz kommt es zur Wasser- und Kochsalzretention.

Da das Wasser extrarenal leichter abgegeben werden kann als das NaCl, entwickelt sich meist eine Hypersalämie, die eine wesentliche Ursache der eklamptischen Urämie ist. Die Schwankungen der Cl- und Na-Ionen gehen keineswegs immer miteinander parallel; ausnahmsweise

Ionogramme bei verschiedenen Formen der Uraemie (U)

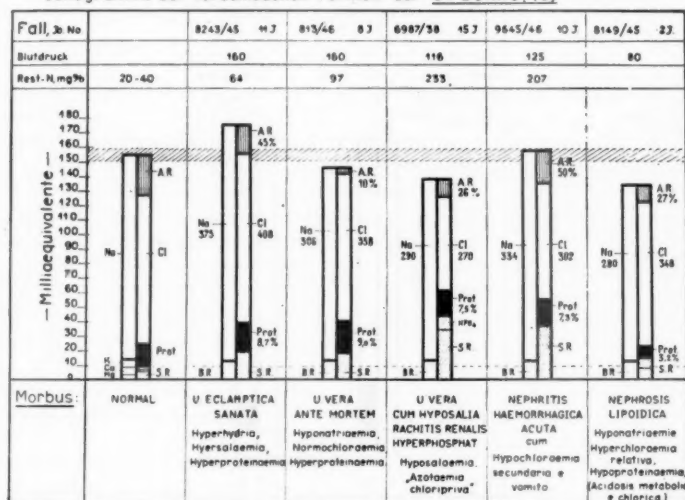


Fig. 3.

können ihre Werte so weit auseinander gehen wie etwa in Fall III der Abbildung, sodass man eine »trockene« Bindung eines Teiles der Cl-Ionen an das Eiweiss annehmen muss.

IV. Störungen des intermediären Stoffwechsels.

Bei Störungen des intermediären Stoffwechsels steigen die organischen Säuren im Plasma stark an (metabolische Acidosis), Alkalireserve und Cl-Wert sinken, um Basen für die organischen Säuren frei zu geben. Es kommt zur grossen Atmung und zur Pseudohypochlorie. Dies ist häufig der Fall beim diabetischen Coma.

V. Hypo- und Hyperglykämie.

Sowohl die Hypo- als auch die Hyperglykämie können toxische Zustände erzeugen; z. B. kommt es bei der Cystinkrankheit einzig durch Dextroseverabreichung per os zu einem hyperglykämischen Schock.

Im konkreten Fall kommt es meist auf verschiedenen Wegen (I bis V) gleichzeitig oder nacheinander zum toxischen Zustand; so ist die Hyposalämie meist mit Exsikkose verbunden oder zum Ausgleich einer Hyperglykämie muss zur Verdünnung des Zucker viel Wasser von den Nieren ausgeschieden werden, was ebenfalls zur Exsikkose führen kann usw. Die rasche Diagnose, welcher Haushalt hauptsächlich gestört ist, ist für die Soforttherapie von entscheidender Bedeutung.

DIABETES MELLITUS U. WILLY, 16 J

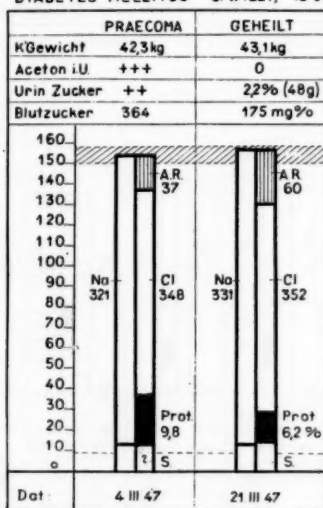


Fig. 4.

Es liegt auf der Hand, dass tiefgreifende Störungen im Haushalt des Wassers, der Na- und der Cl-Ionen als den Hauptelektrolyten der extrazellulären Flüssigkeit sowie des Hauptbrennstoffes Dextrose rasch zu Stoffwechselkatastrophen führen. Zweifellos können auch andere quantitativ weniger wichtige Stoffe zu toxischen Symptomen führen, wenn ihre Konzentration weitgehend von der Norm abweicht. Ich denke dabei an das Ca, an die Phosphate und an das Cholesterin usw.

Es gibt stoffwechselstabile und stoffwechselabile Kinder, mit andern Worten, die Toxikosebereitschaft variiert von Individuum zu Individuum. Wir wissen, dass ein Diabetiker, ein Cystinkranker, ein chlor-natriumlables Individuum (*Diabetes insipidus*, *Morbus Addison*) viel rascher toxisch wird als ein gesundes. Zweifellos gibt es daneben leichtere Formen der Stoffwechselbarkeit, die wir heute noch nicht recht erfassen können. Ich erinnere an die grosse Schar der Acetonaemiker, der Fieberkinder usw. Ferner ist es eine Erfahrungstatsache, dass manche Säuglinge, welche eine Stoffwechselkatastrophe überstanden haben, später leicht wieder toxisch werden. Wohl mag die Stoffwechselkatastrophe für eine gewisse Zeit die Widerstandskraft des Organismus gegen Stoffwechselstörungen geschwächt haben; es ist aber sehr gut denkbar, dass eine primäre Stoffwechselbarkeit schon an der ersten Katastrophe mitschuldig war. Interessant ist, dass solche stoffwechselbare Kinder oft degenerative Stigmata aufweisen, z. B. grosse Köpfe, vertiefte *Impressiones digitatae* (*dyskraniale Typen*), Muskelhypotonie usw.

Dr. E. Gorter, Leyden, Netherlands.

A review of all cases of alimentary toxicosis that have been observed from 1916 to 1937 in Leyden's pediatric clinic, is given. From a total of 192:94 children died.

When grouping the cases according to the months of the year a high peak in the summer months is seen (table 1).

When grouping the cases according to age, it appears that most cases occur in the first half of the first year (table 2).

The total infant mortality in Leyden with 70 to 80 000 inhabitants had dropped before the war from 22.1 % to 1.68 %. After the war and the period of famine, conditions were so bad, that mortality has risen to 9.2 %, almost the number of the period 1906—1910 (table 5).

When grouping the total cases of alimentary toxicosis that have been observed from June 1945 to June 1947 (table 3) we notice a total of 60 cases of alimentary toxicosis in two years with a total number of deaths of 17. The distribution according to months of the year shows again a rather prolonged summer peak. If we group the 17 cases deaths from alimentary toxicosis that have occurred from June 1945 to June 1947, the same prevalence for the first part of the first year is noticed (table 4).

PLENARY SESSION

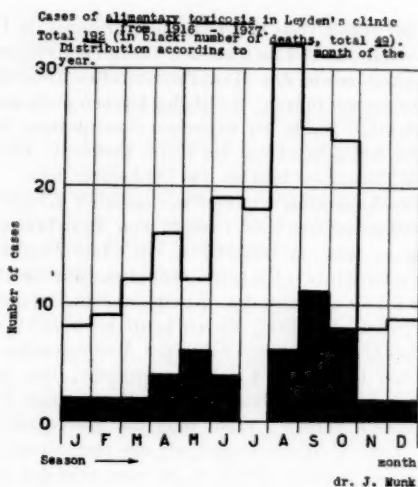


Table 1.

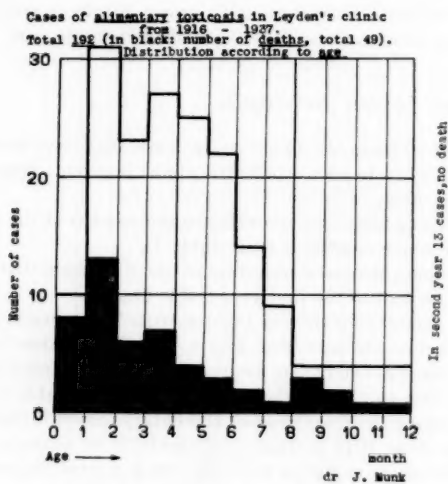


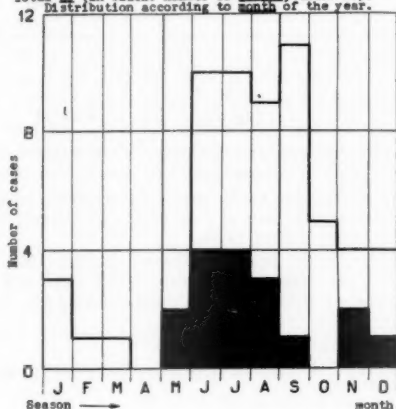
Table 2.

It is interesting to observe how always there exists a relation between the total numbers of infant mortality during the first year of life and the most important causes of death.

Cases of alimentary toxicosis in Leyden's clinic
from June 1945 - June 1947.

Total 60 (in black: number of deaths, total 17).

Distribution according to month of the year.



dr. T.G.Boonacker

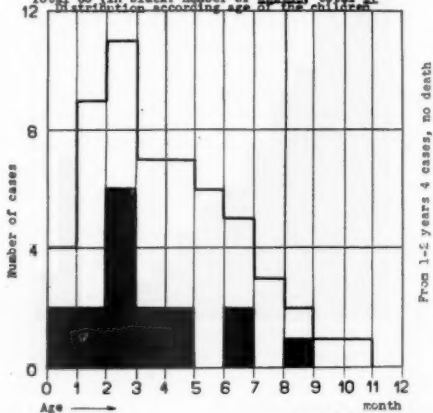
dr. C.A.Winkel

Table 3.

Cases of alimentary toxicosis in Leyden's clinic
from June 1945 - June 1947.

Total 60 (in black: number of deaths, total 17)

Distribution according to age of the children.



dr. T.G.Boonacker

dr. C.A.Winkel

Table 4.

From the Report of the inquiry performed under the auspices of the League of Nations in different towns and rural districts of Europe during 1927, one may derive that the following rules hold good:

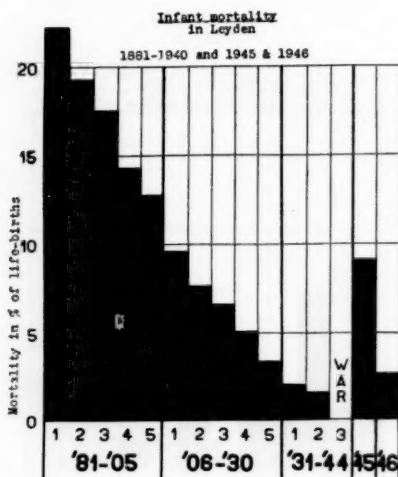
Mortality	% of life-births	Dig. dist.	Still-births & first week
Low	3.5—4.9	<5 %	66 % of total
Intermediate	5.0—6.9	15 %	50 % " "
High	7.0—10.0 and >10	30 %	33 % " "

Low: very few deaths by digestive disturbances, prevalence of infectious diseases, preponderance of obstetrical mortality: 2/3 of total.

Intermediate: more deaths due to digestive disturbances, same importance of infectious diseases; smaller part of total deaths due to still-births and deaths during the first week: 1/2 of total.

High: many more deaths by diarrheal disorders, alimentary toxicosis (high peak in summer) and marasmus, also more infections and respiratory disorders, same total of still births and deaths during the first week: 1/3 of total.

These rules apply equally well to a comparison of the infant mortality in Leyden in 1881, 1936 and again 1945/46.



1881—1885.....	22.1 %	1906—1910.....	9.5 %	1931—1935.....	2.20 %
1886—1890.....	19.3 %	1911—1915.....	7.62 %	1936—1940.....	1.68 %
1891—1895.....	17.5 %	1916—1920.....	6.70 %	1941—1945	unreliable
1896—1900.....	14.3 %	1921—1925.....	5.04 %	1945	9.2 %
1901—1905.....	12.8 %	1926—1930.....	3.34 %	1946	2.78 %

Table 5.

Doctor **Felix Hurtado**, Habana, Cuba.

1. *Terminología.*

El nombre de alimentary toxicosis, no es adecuado, puesto que presupone la participación directa del alimento en todos los casos de esta síndrome, cuando en verdad su patogenia es compleja y el alimento en sí, solo es responsable en un reducido tanto por ciento de los casos.

La infección es indiscutiblemente un factor etiológico en estos trastornos nutritivos agudos del lactante y la intoxicación es también factor patogénico de primer orden: determinando ambos: la infección y la intoxicación, la producción de graves alteraciones metabólicas que le dan carácter clínico a este síndrome adoptando distintas modalidades clínicas, pero que pueden sin embargo, incluirse en dos grandes grupos:

- A. Síndrome circulatorio.
- B. Síndrome nerviosos.

Mantenemos por lo tanto, las ventajas del término toxinfeción aguda en el lactante.

2. En el *síndrome circulatorio*, son características los elementos del shock periférico, en cuya producción intervienen principalmente la deshidratación como factor patogénico.

El síndrome diarrea es la principal causa de este fenómeno, Pero a veces el shock se instala sin evidencia alguna de deshidratación, sin que el enfermo haya tenido diarreas, lo que indica, que es un factor metabólico de otra naturaleza el agente desencadenante del fenómeno circulatorio. Parte muy destacada juega en esta variedad el estado nutricional del paciente, muy particularmente en lo referente a déficit vitamínico, principalmente a la carencia de vitamina B1.

También es de notar la gran resistencia de algunos niños en los que el shock periférico no se presenta y el síndrome de deshidratación aguda no llega a instalarse a pesar de un crecido número de diarreas en el día.

3. Son factores principales en la producción de estos cuadros, la pérdida de electrolitos que el sujeto sufre en la deshidratación y ello origina naturalmente, graves trastornos humorales, que hemos venido estudiando desde 1930 con el nombre de síndrome humoral, muy particularmente en los síndromos de desequilibrio ácido-básico: acidosis y alcalosis observados en el curso de estas toxemias.

4. El sistema nervioso del niño, tanto mas cuanto mas pequeño es, sufre grandemente en el transcurso de estos síndromos de toxinfeción aguda, dándole al cuadro una gravedad-extrema.

La convulsión es el síntoma mas alarmante, se instala súbitamente, a veces como manifestación inicial dentro de una salud aparente o de modo incidioso en el curso de un proceso diarreico.

La encefalitis es la forma anatomo-clínica que desarrollan estos enfermos acompañándose al propio tiempo de graves trastornos metabólicos y síndrome humoral con predominio alcalótico.

Estos cuadros ofrecen una gravedad tan extraordinaria, que elevan la mortalidad sobre el 60 %.

Es interesante señalar aquellos casos en que no obstante la apariencia del síndrome diarreico y fenómenos toxinfeciosos serios, la sintomatología nerviosa no se instala ni en el shock circulatorio tampoco se manifiesta, desenvolviéndose el cuadro dentro de una evolución benigna. Así ocurre con gran frecuencia en los sujetos bien alimentados con óptima nutrición.

Algunos tipos de infección como las ocurridas por el género *Shigella*, tienen tendencia a la instalación precoz del síndrome nervioso.

5. En el estudio etio-patológico de esta síndrome de toxinfeción, se hace necesario tener en cuenta: A) el sujeto (constitución), el terreno de que hablan algunos autores; B) ambiente, especialmente climático (temperaturas, humedad, etc.); C) higiene de la alimentación (régimen alimenticio balanceado, equilibrado, etc.); D) Control de las enfermedades infecciosas dominables por vacunación.

6. No obstante todo cuanto se ha investigado en el sentido del esclarecimiento etiopatogénico de la toxicosis o toxinfeción aguda del lactante, como nosotros lo denominamos, hay todavía en la actualidad muchos puntos oscuros y aún de una interpretación contradictoria.

7. No cabe duda que hasta el presente el tratamiento sintomático del síndrome correspondiente es lo único que podemos manejar acertadamente con tal de que convenimos nuestra terapéutica de una manera paralela al concepto fisiopatológico de estos trastornos, lo que nos hace recomendar en cuanto a la rehidratación se refiere, una técnica especialmente controlada que nos permita el manejo preciso del electrolito en déficit correspondiente.

También insistimos en las ventajas terapéuticas de lo que hemos dado en llamar climatoterapia, dirigida o artificial, lo cual nos permitirá utilizando la refrigeración moderna, preparar una atmósfera conveniente al sujeto enfermo.

8. Finalmente reproducimos aquí nuestra recomendación en el Congreso Panamericano de Pediatría, que acabamos de celebrar en la ciudad de Washington:

Mantener en el programa de la próxima reunión internacional el interesante tópico de la toxinfeción aguda del lactante.

Designar una comisión internacional que organice un programa especialmente destinado a realizar una investigación coordinada que permita en su día realizar un amplio simposium sobre esta materia.

Dr **Maurice Lust**, Bruxelles, Belgique: *Le syndrome toxémique du nourrisson. Toxémic syndrome in Infancy.*

Les statistiques officielles, donnant les causes des décès, classent sous une rubrique spéciale, les décès provoqués par la diarrhée.

Les causes des décès, enregistrées par les statisticiens, sont celles indiquées par les médecins traitants.

Ayant compulsé les déclarations de décès, où la mort était attribuée à la diarrhée, j'ai été frappé de constater deux choses: ce diagnostic n'est posé que pour des nourrissons, jamais pour des grands enfants ou des adultes, ensuite tous les décès provoqués par la diarrhée se sont produits au domicile des parents, jamais dans les hopitaux d'enfants.

Lorsqu'on compare les statistiques dressées par la plupart des pays depuis cinquante ans, on constate que le taux des décès provoqués par la diarrhée diminue. Les sociologues et les hygiénistes attribuent cette réduction de la mortalité par diarrhée à l'amélioration de l'hygiène générale et à la meilleure application de l'hygiène infantile. Les sociologues et les hygiénistes se trompent en émettant cette affirmation. La réduction du nombre de décès attribués à la diarrhée provient de ce que les médecins, mieux au courant de la pathologie infantile, font des diagnostics plus exacts, recherchent et trouvent souvent la maladie causale et n'attribuent plus à la diarrhée que l'importance qu'elle mérite.

Lorsqu'un médecin voit un de ses patients, grand enfant ou adulte, mourir de fièvre typhoïde, de dysenterie, de choléra ou de toute autre affection, dans laquelle les troubles intestinaux sont importants, il ne se contente pas d'indiquer sur le certificat de décès «diarrhée». Il ne comment, ou n'ose commettre, ce diagnostic basé sur un seul signe clinique que pour les nourrissons. Les pouvoirs publics et les services d'hygiène entérinent cette insuffisance de diagnostic.

Quasi toutes les affections, infectieuses ou non, peuvent s'accompagner de diarrhée chez le nourrisson, surtout lorsque celui-ci ne reçoit pas une alimentation parfaitement adéquate, c'est-à-dire du lait maternel. Il faut souligner que presque toujours les signes de dyspepsie sont les premières manifestations cliniques d'une affection bénigne ou grave chez le nourrisson. La dyspepsie précède tous les autres signes cliniques, parfois de plusieurs jours. Il n'est pas, conséquemment, étonnant qu'un médecin insuffisamment averti, pose un diagnostic de diarrhée sans attendre les signes cliniques de la maladie causale.

Si l'enfant meurt, sans présenter de signe manifeste de la maladie causale, le médecin conserve le diagnostic de diarrhée comme cause de décès.

Nous trouvons dans la rubrique d'enfants morts de diarrhée, des cas du syndrome qui nous occupe, des cas de malformations congénitales du système digestif, de débilité congénitale et de nombreuses autres affections.

Cette insuffisance de diagnostic n'est pas commise par les pédiâtres ni au domicile de l'enfant, ni à l'hôpital. Il semblerait donc inutile de la rappeler dans cette assemblée. Si j'ai cru devoir le faire, c'est que de plus en plus le diagnostic de diarrhée grave est remplacé par des termes qui sont différents d'un médecin à l'autre. L'énumération des appellations utilisées serait fastidieuse. Comme les statisticiens ne sont pas toujours versés dans les synonymes médicaux, ils font des classements au petit bonheur et faussent ainsi tous les chiffres.

Le temps très court, qui est réparti aux orateurs, ne permet pas à chacun d'exposer en détail les connaissances et recherches concernant ce syndrome. J'ai laissé cette mission à mes collègues et j'ai cru utile de me limiter à voir si nous pouvions trouver une terminologie acceptable provisoirement par tous.

Rappelons ici que ce fut le Docteur Parrish, qui, le premier, en 1826, décrivit l'affection que nous discutons ici. Il eut le tort de la confondre avec le choléra asiatique, ce qui l'amena à lui donner le nom de «cholera infantile».

Ce terme désuet est parfois encore utilisé dans certaines publications.

Donner une acception différente à un même mot ou employer différents termes pour désigner un même objet amène fatalement de la confusion. Si le même vêtement est appelé veston par les uns, et par d'autres rédingote, il ne sera jamais possible de s'entendre. Avant de commencer toute discussion, il est indispensable de se mettre d'accord sur l'objet de la discussion et de lui donner un nom, tout au moins provisoire, quitte à le rectifier ultérieurement. Ce n'est pas une raison parce que la mode changera que nous devons nous promener tout nu.

Le Docteur Mc Intosh, Président du Comité Scientifique du Congrès, a bien voulu me dire que le titre de la question mise à l'ordre du jour fut beaucoup discuté par le Comité. Dans les publications scientifiques l'affection que nous discutons est consignée sous un nombre invraisemblable de titres. On arrive à une telle confusion, que la même question, mise à l'ordre du jour du Congrès des Pédiâtres de Langue Française en 1949, est indiquée sous une autre appellation que celle utilisée aujourd'hui.

L'état toxique, accompagné généralement de déshydratation aiguë et de dyspepsie grave, ne constitue certainement pas une maladie autonome, puisque nous pouvons le constater comme complication de nombreuses maladies infectieuses ou non. C'est un syndrome clinique qui complice diverses maladies du nourrisson.

Si nous sommes d'accord sur ce point, il serait nécessaire de le dire dans notre appellation afin d'attirer l'attention des médecins de famille. Ainsi nous obtiendrons, lorsqu'ils rencontrent une dyspepsie grave avec un état toxique, qu'ils cherchent la maladie causale et ne se contentent pas d'essayer de guérir la diarrhée par des modifications de régime, ou des médicaments constipants.

Afin de pouvoir classer ce syndrome dans la nosologie générale, au substantif «syndrome» nous devons ajouter un qualificatif caractérisant l'étiologie, la pathogénie ou la symptomatologie de ce syndrome.

Etiologie:

Les médecins du siècle dernier, quoique souvent d'excellents cliniciens et possédant de merveilleux dons d'observation, n'ayant pas à leur disposition les techniques de recherches que nous possédons, ont commis l'erreur de confondre la cause avec un simple signe de défense de l'organisme. Ils ont considéré, chez le nourrisson, la diarrhée ou les vomissements comme une maladie. Voulant trouver une cause à la maladie, ils l'ont attribuée à une intoxication alimentaire ou à une infection d'origine alimentaire.

La cause des dyspepsies attribuées à l'alimentation fut l'objet d'un nombre incommensurable de mémoires, rapports et articles.

On incrima d'abord une infection amenée par le lait. Ce fut l'époque des recherches bactériologiques, dirigées spécialement sur les flores microbiennes de l'intestin. De nombreux chercheurs ont espéré trouver le microbe causal de la «gastro-entérite» du nourrisson.

On accusa ensuite les divers composants du lait. Chacun des composants du lait fut tour à tour accusé des pires méfaits. Il y eut l'époque du poison caséine, celle du poison graisse, celle du poison lactose et même du lacto-sérum. Et l'on préconisa pour éviter l'intoxication alimentaire des préparations plus compliquées et plus alambiquées les unes que les autres.

Les médecins de cette époque attribuaient à une affection gastro-intestinale, la diarrhée provoquant l'état toxique et la déshydratation, et parlaient d'intoxication alimentaire.

Il est évident que des dyspepsies, parfois graves, peuvent provenir des fautes de régime: le sevrage brusque, une alimentation longtemps carencée, ou indigeste, par exemple, mais ces erreurs de régime n'entraînent pas, sans une autre cause, un état toxique ou de la déshydratation aiguë. Leur aboutissement est la dénutrition aiguë ou chronique, donc un état de moindre résistance, qui les rend plus aptes, lors d'une infection parentérale, à faire un syndrome toxique.

Ce qui permettait à cette époque l'hypothèse d'une origine alimentaire, était le fait que la trilogie: dyspepsie, état toxique et déshydratation était l'apanage d'enfants nourris, souvent mal nourris, au lait de vache et se voyait surtout pendant les mois chauds de l'année.

Nous savons maintenant, à la suite des études de pathologie géographique, que certaines épidémies sont favorisées par le climat et les saisons. Le syndrome, caractérisé par l'état toxique accompagné de dés-

hydratation aiguë et de dyspepsie grave, se voit beaucoup plus fréquemment dans certaines contrées que dans d'autres. Le taux de mortalité est différent d'une année à l'autre, sans que la léthalité soit toujours en rapport avec la température. Nous avons pu constater que le syndrome toxi-infectieux épidémique des nouveaux-nés peut se voir chez des enfants correctement nourris au sein maternel et que des enfants atteints d'un état toxique très grave, présentent parfois peu de signes de dyspepsie, tandis que d'autres émettaient des vomissements et des diarrhées incoercibles.

Nous rencontrons parfois chez les grands enfants de véritables intoxications alimentaires, apportées par les aliments. Celles-ci résultent de l'ingestion d'aliments toxiques: champignons ou aliments avariés par exemple. Il ne peut être question de ces sortes d'intoxication alimentaire chez le nourrisson de quelques mois qui consomme du lait de vache. La caractéristique du lait étant, par son acidification spontanée, d'empêcher l'autolyse des protides et donc la formation de corps toxiques. Le lait aigri se conserve très longtemps sans se corrompre, il est consommé par une grande partie du genre humain, il est très utilisé comme aliment de réalimentation en diététique infantile. Un excès d'acidité peut, comme nous l'avons constaté dans nos expériences, provoquer des dyspepsies, mais jamais de syndrome toxique.

Les dyspepsies légères ou graves proviennent d'une diminution de la tolérance alimentaire, par réduction du pouvoir digestif ou d'assimilation, sans que nous ne sachions le processus qui intervient pour provoquer cette réduction. En émettant cette constatation clinique, nous n'avons pas élucidé le problème.

Nous croyons que les termes, parfois utilisés pour désigner le syndrome, d'intoxication alimentaire ou de toxicose alimentaire doivent être délaissés.

Ces appellations sont certainement fausses puisque la cause de l'affection n'est jamais alimentaire. Elle ne résulte pas d'un toxique amené avec ou par un aliment, ni d'une altération des aliments avant son ingestion ou au cours de leur transit dans le tube intestinal. En outre ils offrent le grand danger de laisser supposer que la thérapeutique est d'ordre diététique. Nous voyons trop souvent des médecins non avertis y avoir recours au grand dam des petits malades.

Il est regrettable que Franck et Abranson de New-York, qui ont parfaitement individualisé le syndrome toxi-infectieux épidémique du nouveau-né, aient cru devoir lui donner l'appellation de «epidemic diarrhea of the new-born» alors que divers auteurs, comme nous, ont constaté des cas sans diarrhée. Le diagnostic de ces cas sera fait aisément par les pédiâtres avertis, mais, par cette terminologie erronée, on fausse la compréhension des jeunes et des médecins de famille.

Pathogénie:

La pathogénie de ce syndrome est encore très controversée. Nous avons fait des progrès très importants depuis que l'on attribuait ce syndrome à des humeurs peccantes ou à une intoxication alimentaire.

Les travaux français d'Hutinel, de Reilly et ses collaborateurs, de Marquezy et Melle Pladet sur le syndrome malin dans les maladies infectieuses ont montré l'importance que joue, dans ce syndrome, le système nerveux sympathique. Ces derniers ont constaté, qu'il est possible de déterminer, chez l'animal, par irritation du sympathique des désordres viscéraux et nerveux absolument superposables aux constatations anatomiques que l'on peut faire aux autopsies des malades morts d'un syndrome malin.

Certains voudraient voir dans l'atteinte du système neuro-végétatif, le fait capital et primordial de la pathogénie du syndrome que nous discutons. Aucune expérience formelle ne permet encore cette conclusion. Il nous semble prématuré de confondre le syndrome malin survenant à la suite des affections telles la diphtérie, la rougeole, la coqueluche ou la scarlatine, avec le syndrome que nous discutons.

Quoiqu'une atteinte du système neuro-végétatif soit très probable, il reste encore à préciser par quel processus cette atteinte se produit, s'il est provoqué par des toxines amenées par le courant sanguin ou par des modifications humorales primitives à cette atteinte.

Lesné fut le premier à rapprocher ce syndrome du choc anaphylactique de Richet. Il a montré, avec Lucien Dreyfus, qu'on peut supprimer le choc anaphylactique en anesthésiant les animaux. Marquezy a constaté que les désordres viscéraux et nerveux, caractéristiques du syndrome malin, ne se produisaient pas après irritation du sympathique, lorsque les animaux étaient anesthésiés au préalable.

Il est donc possible que le syndrome discuté résulte d'un processus apparenté à l'anaphylaxie ou à l'allergie. Il reste encore à préciser son rôle et à trouver quels sont les allergènes qui provoquent ce phénomène de choc et leur mode d'action.

Les modifications humorales habituellement constatées se retrouvent dans d'autres affections et ne peuvent être utilisées pour caractériser le syndrome. Il est très possible, comme dans de nombreuses autres affections, que ce soient les modifications humorales qui déclenchent ici également les divers phénomènes pathologiques.

Johnson et Bothman ont constaté, par l'étude de la réserve alcaline, que l'acidose est présente avant l'apparition des selles diarrhéiques, la diarrhée ne faisant ultérieurement qu'accentuer cette acidose. Il serait possible de juguler l'affection, par une thérapeutique appropriée, avant l'apparition de l'état grave, ce qui serait très en faveur d'une pathogénie humorale primitive.

Les perturbations électrolytiques et les modifications de perméabilité

des membranes cellulaires aux électrolytes ont été montrées par les travaux de Ribadeau-Dumas et de ses élèves en France et par Fanconi de Zurich et ses élèves. Plusieurs écoles américaines ont publié de très belles études sur ces modifications.

L'état actuel de ces travaux, s'ils sont d'une grande aide pour notre thérapeutique, n'éclairent pas encore complètement la pathogénie du syndrome.

Il semble difficile, dans l'état actuel de nos connaissances, de définir la pathogénie exacte de ce syndrome. En conséquence, pour ne pas créer de rivalité d'école, il est préférable de ne pas introduire dans le titre une indication pathogénique.

Symptomatologie:

Tous les auteurs sont d'accord sur les symptômes cardinaux du syndrome: état toxique, déshydratation aiguë et dyspepsie grave. Le symptôme clinique capital, sans lequel le syndrome n'existe pas, est l'état toxique, il caractérise nettement le syndrome que nous discutons. Les auteurs ne sont pas encore d'accord sur la primauté dans le temps qu'il faut accorder à l'état toxique et à la déshydratation. Certains, dont Marriott, estiment que l'état toxique résulte de la déshydratation, ce qui est possible, mais pas démontré.

Il est très difficile, dans l'état actuel de nos connaissances, de savoir si nous devons rattacher au syndrome que nous discutons, celui qui fut décrit par Ombredanne et appelé par lui «syndrome pâleur et hyperthermie». Complication que l'on rencontre parfois et, uniquement chez le nourrisson, après une intervention chirurgicale.

Conclusion:

Le terme de toxicose, dont je n'oserais donner la paternité à personne, de peur de commettre une erreur, ne me plait guère, parce qu'il semble faire de ce syndrome une maladie, ce que nous savons erroné.

Je vous propose à titre provisoire, le terme de «syndrome toxémique du nourrisson». «Toxémie syndrome in Infancy.»

Je reconnais parfaitement que cette appellation laisse beaucoup à désirer. Si quelqu'un veut proposer un autre terme, qui soit préférable, je suis tout prêt à l'adopter. Je crois indispensable, dans un but de clarification, d'enseignement et de statistique que nous utilisions tous le même terme pour désigner ce syndrome.

Dr. K. Biering-Sørensen, Copenhagen, Denmark.

The malignant epidemic form of Gastro-enteritis which in recent years has occurred in pediatric and maternity departments in several countries, had not been observed in Scandinavia prior to the last 4—5 years.

Several epidemics have been observed in children's homes and pediatric clinics in Copenhagen, Denmark since December 1943. It would seem that the disease observed here has been of the same nature, clinically and epidemiologically, as the epidemic diarrhea of the newborns, except that it also occurs in older infants up to 9 months of age.

When the disease first appeared, it was of a very malignant character with a high morbidity rate and a mortality rate of more than 50 %. More than 500 infants contracted the disease during a two year period from 1943 to 1945. Since 1945 it would seem that the disease is less severe. A severe outbreak, however, has occurred in Copenhagen during the last few weeks.

The etiology and pathogenesis of the disease have not been established, but many factors suggest that the infection may be a general one with secondary gastrointestinal manifestations and that it may be viral in origin.

Post-mortem examinations have not revealed any pathologic changes which can be considered characteristic. As a rule the findings consist merely of some degree of fatty degeneration of the liver, with at times a complicating bronchitis, bronchopneumonia or otitis media.

In many instances the clinical findings suggested the possibility that changes in the vegetative centers of the brain stem might be the primary disturbance. Additional support was given to this hypothesis by the finding of increased numbers of cells in the spinal fluids of several babies.¹

In order to investigate this possibility a thorough examination of the central nervous system was made in 32 of the infants who died of this disease. In 8 or 25 per cent of the infants, meningo-encephalitis was observed on microscopic examination. Grossly there was merely congestion of the pial and cerebral vessels.

In 18 or 56 per cent of the infants, there was evidence of meningitis only and in the remaining 6 cases neither the brain nor leptomeninges showed any round-cell infiltration but merely congestion and slight edema of the pia and the brain tissue.

Whether the gastro intestinal manifestations are the result of a primary encephalitis or are secondary to a general infection or intoxication is not apparent from these observations or from the reports of other authors.

As pointed out by Dr. Kerpel-Fronius, the cerebral changes, whether primary or secondary, may be a very important factor in the pathogenesis of the intoxication in infants with severe diarrhea.

¹ Reported in more detail by CHRISTENSEN, ERRA and BIERING-SØRENSEN, K., *Acta Pathologica* XXIII, p. 395, 1946.

Plenary Session—Congenital Heart Disease.

RELATOR.

Congenital Heart Disease.

Por **Agustin Castellanos**, Havana, Cuba.

Clasificación.

Tomando como bases la clasificación de Variot (1921), la de Abbott (1924), y la de Cossio (1938), nosotros con el Dr. R. Pérez de los Reyes las hemos agrupado en la siguiente forma:

Grupo sin cianosis.

Con soplos:

1. Estrechez aórtica orificial.
2. Coartación de la aorta.
3. Comunicación inter-ventricular.
4. Comunicación inter-auricular.
5. Persistencia del conducto arterio-venoso.
6. Bilogía tipo I.
7. Estrechez pulmonar grado I.

Sin soplos:

8. Dextrocardia simple.
9. Hipertrofia cardíaca idiopática.
10. Bloqueo cardíaco congénito.
11. Anomalías de los vasos coronarios.
12. Cayado aórtico a la derecha.
13. Anomalías de las grandes venas.
14. Bicúspides aórticas y fenestración.
15. Microcardia.
16. Agenesia total de una de las grandes ramas de la arteria pulmonar.

Grupo con cianosis.

Con soplos:

17. Estrechez pulmonar grados II y III.
18. Bilogías tipos II y III.
19. Trilogía de Fallot.
20. Tetralogía de Fallot.

21. Tetralogía de Eisenmenger.
 22. Tronco arterial persistente.
 23. Enfermedad de Corvisart.
 24. Transposición total de los grandes vasos con defectos septales.
 25. Estrechez y atresia tricúspidea.
 26. Insuficiencia tricúspidea.
 27. Pentalogía: Tetralogía de Fallot:
 - a) con comunicación inter-auricular.
 - b) con conducto arterio-venoso.
 28. Enfermedad de Lutembacher.
- Sin soplos:
29. Transposición total de los grandes vasos sin defecto interventricular.
 30. Corazón bilocular.
 31. Corazón trilocular.
 32. Defectos variados.

Llamamos »bilogías» a la asociación de la comunicación inter-ventricular con la estenosis pulmonar. Hacemos tres grandes tipos:

- Tipo I.* Gran comunicación inter-ventricular con ligera estenosis de la pulmonar.
- Tipo II.* Gran estenosis de la arteria pulmonar con ligera comunicación inter-ventricular.
- Tipo III.* Gran estenosis pulmonar con gran comunicación inter-ventricular.

Llamamos »Pentalogía» a la asociación de tetralogía de Fallot con comunicación inter-auricular: *Tipo A*; o con el conducto arterio-venoso: *Tipo B*.

Hacemos tres grupos de estenosis pulmonares según el grado de la misma. El grado I es el más ligero, sin cianosis. El grado II y el III, tienen siempre cianosis por ser muy cerrada la estenosis.

Colocamos en la clasificación a la Microcardia porque hoy en día está demostrado por los trabajos de Master y otros, que existe y que ella es causa de trastornos circulatorios. Con Master creemos que es congénita.

Las anomalías de las grandes venas cardíacas, especialmente la persistencia de la vena cava superior izquierda, es muy frecuente.

La agenesia total de una de las ramas de la arteria pulmonar existe cuando hay agenesia pulmonar.

El objeto de nuestra clasificación es hacer una serie de grupos y permitir al médico, de acuerdo con la presencia o ausencia de soplos o de cianosis, orientarse hacia un diagnóstico anatómico. La orientación lo conduce a una sección de la clasificación y entonces con el concurso de los medios auxiliares de investigación hace el diagnóstico definitivo.

Frecuencia.

En las estadísticas la frecuencia de los distintos tipos de cardiopatías varía según sean hechas en vida de los enfermos o en la mesa de autopsias. También varían según sean hechas en la infancia o en la edad adulta.

Desde fines de 1937 hasta Abril de 1947 hemos estudiado de un modo completo, incluso angio-cardiográficamente, a 204 casos de cardiopatía congénita en el niño. No se incluyen en esta cifra los casos mal estudiados, ya sea por la corta evolución de la enfermedad, que no da tiempo a todos los exámenes, o a la falta de cooperación de la familia.

Vamos a dividir la estadística en dos grupos:

I. Lesiones únicas o simples:

	Casos
Estenosis pulmonar (de los tres grados).....	6
Roger.....	52
Coarctación de la aorta.....	2
Comunicación inter-auricular.....	11
Estenosis aórtica.....	2
Conducto arterio-venoso.....	8
Hipertrofia cardíaca idiopática.....	2
Estenosis de los troncos venosos innominados.....	2
Insuficiencia tricuspídea.....	1
Agenesia de una de las ramas de la arteria pulmonar	1
Insuficiencia aórtica congénita.....	1

En total 88

II. Lesiones combinadas:

Casos

Tetralogía de Fallot.....	33
Tetralogía de Fallot con conducto arteriovenoso	2
Tetralogía de Fallot con comunicación interauricular .	2
Tetralogía de Fallot con comunicación interauricular más Cava superior izquierda.....	1
Tetralogía de Fallot con dextrocardia.....	1
Bilogía (de los tres tipos).....	30
Enfermedad de Corvisart.....	6
Trilogía de Fallot.....	10
Dextrocardia con Roger y situs inversus.....	1
Dextrocardia con Trilogía.....	1
Dextrocardia con estenosis pulmonar y com. interauri- cular.....	2
Dextrocardia con bilogía.....	1
Dextrocardia con com. interventricular y aneurisma pulmonar.....	1
Corazón trilocular monovenricular con doble cava su- perior, comunicación inter-auricular.....	1
Corazón trilocular monovenricular con aorta a la de- recha, cava superior izquierda y cava inferior izq.	1
Corazón trilocular monovenricular con com. inter-auri- cular, doble cava superior izq. y estenosis pulmonar	1
Corazón trilocular monovenricular con com. interauri- cular.....	1
Corazón trilocular monovenricular con conducto ar- terio-venoso	1
Corazón trilocular monoauricular.....	1
Estenosis pulmonar con comunicación inter-auricular	1
Comunicación interventricular con inter-auricular.....	7
Comunicación interventricular con aorta a la derecha	1
Bilogía con cava-superior izquierda.....	1
Coartación aórtica con conducto arterio-venoso.....	1
Coartación aórtica con com. inter-auricular, aorta a la derecha y estenosis pulmonar.....	1
Comunicación inter-auricular con conducto arterio-ve- noso.....	2

	Casos
Comunicación inter-auricular con cava superior izquierda	1
Transposición total con conducto arterio-venoso y con comunicación inter-ventricular.....	1
Transposición total con comunicación inter-ventricular	1
Tronco arterial persistente con comunicación interven-tricular.....	1
Atresia tricuspídea con comunicación inter-auricular y com. inter-ventricular.....	1

En total 116

En resumen: lesiones simples: 88 casos

lesiones combinadas: 116 casos.

Las formas sin cianosis son más frecuentes que las que tienen cianosis. En la estadística del Dr. Rodolfo Pérez de los Reyes y Dr. Horacio de la Torre, del Departamento de Cardiología del Hospital Municipal de Infancia de La Habana, entre 330 casos, 200 no tenían cianosis y 130 sí la tenían.

De las formas cianóticas la más frecuente es la Tetralogía de Fallot.

De las formas acianóticas la más frecuente es la enfermedad de Roger, siguiendo en frecuencia decreciente la bilogía tipo I, es decir, gran comunicación inter-ventricular con ligera estenosis de la arteria pulmonar.

Asociación con otras anomalías somáticas.

Frecuentemente los pacientes afectados de malformaciones cardíacas, tiene otras anomalías de desarrollo, hipertrofia del timo, mongolismo, espina bífida, imperforación anal, riñón poliquístico, angiomas, anisofthalmias, acondroplasia, pie varo equino, polidactilia, fistulas ano-vaginales, mixedema congénito, dextrocardia, hemivértebras con escoliosis, labio leporino, catarata congénita, sickle-cell anemia, etc.

Nos ocuparemos especialmente de la sickle-cell anemia, del mongolismo y de la hipertrofia del timo.

Domagrach y Green, de Boston, encontraron que en los cardiopatas congénitos el 5.8 % tenían sicklelemla.

K. Brousseau encontró que el 20 % de los mongolianos tenían defectos cardíacos. En las estadísticas de nosotros el 7 % de los cardiopatas congénitos tienen mongolismo.

En cuanto al timo el 5 % de nuestros casos tienen hipertrofia del timo bien ostensible.

Frecuencia de la sífilis.

En la estadística de Pérez de los Reyes y H. de la Torre, de 330 casos habían 9 casos ligados a la sífilis. En 4 casos había reacciones serológicas positivas. En 5 casos la positividad de la reacción recayó en los padres.

Etiopatogenia.

Este estudio no se ha considerado en toda la importancia que tiene ya que un gran número de malformaciones cardíacas son graves y quedan completamente fuera del control del médico.

Desde el punto de vista etiológico podemos decir que hay dos clases de malformaciones cardiovasculares:

10. Las que se deben a infecciones cardíacas intra-uterinas (cardio-valvulitis fetales, endocarditis fetales, etc.).

20. Las que se deben a detención del desarrollo de las estructuras cardio-vasculares.

Las primeras tienen aspectos histológicos definidos y su etiología es variable. Las segundas se discuten.

La detención del desarrollo del corazón embrionario se ha querido explicar por la herencia.

Otros invocan la influencia de la sífilis. El papel de la sífilis ha sido señalado por la Escuela francesa sobretodo, pues desde Fournier, Bricout, Grenet, Laubry, y Pezzi, etc., se viene insistiendo en ella. Según estos autores, el treponema puede producir un trastorno profundo en la evolución de los tejidos del embrión ya sea actuando sobre los elementos plasmodiales sin edificar lesiones histológicamente típicas o ya asociadas a esas lesiones.

En este aspecto la etiopatogenia de las cardiopatías congénitas se confunde con las de otras malformaciones: nerviosas, renales, oculares, etc.

Esto explica la frecuencia relativamente elevada de casos de cardiopatías congénitas que tienen otras anomalías somáticas, lo cual se interpretaría como si en el fondo ellas tuvieran un origen generalmente común.

El descubrimiento de Gregory, Grebb, de Australia en 1941, comprobado por Swan, en 1944, en el mismo país, viene a explicar una serie de casos cuyo origen permanecía en la oscuridad. Aunque este punto se ha discutido por muchos autores, la mayoría está de acuerdo en considerar que en efecto, la rubeola adquirida en los primeros meses del embarazo debe considerarse como de gran peligro para el feto. Nosotros hicimos una investigación en 25 casos de cardiopatías congénitas y de estos casos, en 2 había habido rubeola en los tres primeros meses de embarazo. Dos lotes de niños sanos, sin defectos congénitos, en número de 50 cada lote, no acusaban antecedentes de enfermedades eruptivas de la madre durante el embarazo, lo cual contrasta con el 6 % de madres que dieron hijos con defectos cardíacos congénitos habiendo adquirido la rubeola en los primeros meses.

El papel de reacciones antígeno-anticuerpo materno-fetales apuntados por Levine hace años, no parece haberse comprobado.

Tampoco se ha aceptado o probado en el ser humano, la deficiencia vitamínica demostrada por Warinsky en los animales de experimentación.

Examen y medios de exploración de los enfermos.

La exploración de los enfermos por los llamados métodos clínicos tiene un gran valor, porque muchas veces ellos solos pueden sospechar o precisar un defecto cardio-vascular congénito.

Es más, a medida que se tiene más experiencia con los métodos especializados de investigación se obtienen datos prácticos que robustecen muchos signos y síntomas clínicos que hasta ahora les daba poco valor.

Tanto la región precordial misma como otras regiones, cuello, extremidades, etc., el hábito general, el estudio de la piel, mucosas, etc., necesita un detenido examen clínico. Algunas veces, la imposibilidad de hacer un diagnóstico lesional exacto o aproximado se debe a un examen clínico deficiente o incompleto.

La determinación de la tensión arterial en las cuatro extremidades es obligatoria en todos los enfermos.

Electrocardiograma. Es un método de rutina y su obtención sistemática permite hacer deducciones y diagnósticos completamente imposibles por otros medios. El hecho de que en muchos casos no permite orientar el diagnóstico de un modo seguro, no invalida esta investigación.

Basta solamente recordar su valor en los bloqueos cardíacos congénitos y en las atresias tricuspídeas para comprender lo que significa para el pediatra y para el cardiólogo en la determinación de ciertos diagnósticos.

Fonocardiograma. Mannheimer, de Estocolmo, ha logrado una técnica que él llama «Fonocardiografía calibrada» la cual logra la inscripción de los ruidos cardíacos con sus distintas amplitud y frecuencia. Esto es el desideratum en el estudio gráfico de los ruidos cardíacos.

Pero aún sin disponer de una técnica tan depurada, el fonocardiograma habitual (estetoscopio o logarítmico) es de utilidad en la infancia bien para precisar características acústicas en casos de auscultación difícil o para dejar constancia gráfica de un hecho acústico que se deja destacar.

Gasometría sanguínea. Este medio de investigación tiene una gran importancia porque permite precisar la patogenia de la cianosis y en otros casos determinar la variación de la lesión en el orden funcional, destacando mejorías o agravaciones según la saturación de oxígeno en la sangre arterial disminuya o aumente.

Han habido contribuciones excelentes sobre esta materia como las hechas por Cossio y Berconsky, de la Argentina.

Más recientemente, Andrés Cournand, utilizando el método del sondaje de la aurícula derecha ha hecho nuevos aportes que por su importancia serán estudiados aparte.

Otros métodos.

Nos referimos aquí a los siguientes:

A. Tiempo de velocidad circulatoria. Además de las aplicaciones generales que tiene en todos los trastornos cardio-vasculares se ha querido aplicar para determinar la existencia de un

defecto septal o de los cabalgamientos de la aorta sobre el septum.

La observación de Puddu, de Roma, los estudios de McGuire y Goldmann, los de W. M. Hitzig, de Luisada, y otros encuentran en los casos de un corto circuito veno-arterial un acortamiento del tiempo de circulación.

B. Flebograma. Se utiliza muchas veces para estudiar los signos acústicos obteniéndolos simultáneamente con el fonocardiograma o en polígrafos.

Tiene valor en bastantes casos, ausencia o poca altura de P en los electrocardiogramas, ritmos de galope y chasquidos mitrales, bloqueos de rama, insuficiencia tricuspídea, etc.

C. Manometría venosa. Tiene las mismas aplicaciones que en cardiopatías y mediastino-patías del adulto así como para determinar la existencia de compresiones de los grandes troncos venosos, etc.

D. Cardiograma y neumocardiograma. Han sido poco estudiados en el diagnóstico de los defectos septales y por eso no tenemos opinión que dar de los mismos

Métodos radiológicos.

1. Ortodiagrama y telecardiograma. La determinación y estudio de la configuración del corazón y de los diámetros cardiacos tiene un valor extraordinario en las malformaciones cardiovasculars ya que los defectos cardiacos congénitos determinan cambios anatómicos de las cavidades como una adaptación a las lesiones existentes. De este modo, la determinación del estado de las cavidades cardiacas refleja indirectamente lo que ocurre en los grandes vasos y en los septum. También permite apreciar las características anatómicas de la aorta y de la arteria pulmonar.

En general, para cada tipo de angiocardopatía congénita existe una silueta cardiaca característica. Esto es aplicable tanto a las formas anatómicas simples como para algunas de carácter complejo.

Sin embargo, es posible observar siluetas cardiacas comunes para la misma malformación. También es posible ver algunos

casos de la misma malformación dando origen a siluetas cardíacas bastante diferentes entre sí.

Por ejemplo, en la estenosis pulmonar aislada o estando asociada a la comunicación inter-ventricular (bilogía de nuestra clasificación) es clásico el saliente del arco medio y la configuración «en sabot». Pues bien, algunos casos de comunicación interauricular también tienen la misma conformación general.

No obstante estas posibilidades, del estudio de la silueta cardíaca se obtienen grandes orientaciones.

Los diámetros cardíacos normales en el niño menor de un año están mal establecidos.

En cuanto a los niños de más edad, tenemos dos trabajos a la vista. Uno es de Otto Riedel y otro el de Díaz-Niehlsen. Los diámetros del primero son menores que los del segundo.

En Cuba las mediciones quedan mejor dentro de las cifras de Díaz-Niehlsen, pues las de Otto Riedel resultan ligeramente pequeñas.

El índice cardio-torácico del recién nacido, lactantes y niños mayores están sólidamente establecido.

2. Angio-cardiografía. Este método de radiografía cardiovascular es aplicable al niño recién nacido y a los adultos.

En términos generales cuanto más pequeño es el niño mejores son las placas radiográficas que se obtienen. Esto es fácil de explicar si se recuerda que el niño cuanto más pequeño es, más radio-transparente resulta por su menor contenido en sales inorgánicas y agua. De este modo, el cuerpo de contraste se destaca mucho más aunque se empleen concentraciones relativamente mucho más bajas.

Su principio consiste en inyectar desde cualquier vena periférica un cuerpo radio-opaco, poco tóxico a gran velocidad, en $1\frac{1}{2}$ segundos aproximadamente. Si se obtiene una placa radiográfica al terminar la inyección se obtiene la imagen de las cavidades derechas y de la arteria pulmonar con sus ramas: este es el «dextro-angio-cardiograma» de Castellanos y Pereiras. El cuerpo radio-opaco después es conducido a la red pulmonar por la corriente sanguínea volviendo después a las cavidades izquierdas. El tiempo que demora el cuerpo radio-opaco en ir de las cavidades

derechas a las izquierdas varía según la edad del niño y según las condiciones fisio-patológicas de cada caso. Cuando se obtiene la placa radiográfica en el momento que el cuerpo radio-opaco está en las cavidades izquierdas y aorta se observan contrastes menores que en el dextro-angio-cardiograma. La imagen de las cavidades izquierdas y de la aorta se llama: «levo-angio-cardiograma» de Castellanos y Pereiras.

La cantidad a inyectar varía de 5 a 6 cc en el recién nacido hasta 50 o 60 cc en el adulto.

La concentración varía entre 15 o 20 % en el recién nacido y niño de pocos meses hasta 75 % en el adulto.

Es importante señalar que los cuerpos radio-opacos existentes en la actualidad son sustancias químicas estables que atraviesan el organismo en forma líquida como si fuese un cuerpo extraño hasta que se eliminan por la secreción urinaria. Estas sustancias se toleran dentro de límites determinados, es decir que hay una dosis y una concentración que puede utilizarse en las exploraciones cardio-vasculares. Esta dosis la llamamos: «dosis angio-cardiográfica». Si se aumenta la cantidad o concentración se obtienen efectos tóxicos que pueden ser graves.

La dosis angio-cardiográfica determina una disminución de la tensión máxima y de la mínima, aumento de la frecuencia del pulso y de la respiración. A los pocos minutos esto desaparece totalmente.

Las dosis tóxicas producen caída vertical de la presión arterial, dilatación cardíaca y gran ingurgitación de las venas periféricas, bradipnea y bradicardia. Si la dosis es mucho mayor hay entonces síncope cardíaco y respiratorio.

Las dosis que recomendamos por el momento son las siguientes:

	Cantidad	Concentración
Recién nacidos:	6 cc	15 al 20 %
Lactantes de 1 año:	12 cc	25 a 30 %
Lactantes de 2 años:	20 cc	35 %
Niños de 4 años:	25 cc	40 a 45 %
Niños de 8 años:	30 cc	50 a 55 %
Niños de 12 años:	35 cc	55 a 60 %

Estas son cantidades aproximadas pues solamente el experimentado puede adaptar las dosis según las condiciones patológicas de cada caso, según el volumen de las cavidades cardíacas (microcardia, o dilatación e hipertrofia, etc.).

En cuanto a las contraindicaciones debemos decir que no debe practicarse en los casos con gran insuficiencia cardíaca. También su práctica está limitada en aquellos casos en que existe gran desviación mediastinal, neumotórax a tensión, quistes congénitos pulmonares gigantes, atelectasias masivas, etc.

Los líquidos radio-opacos son hipertónicos y determinan ligera deshidratación. Es por eso que horas después de la exploración se debe insistir en la ingestión de líquidos.

La exploración angio-cardiográfica tiene dos aspectos. El ideal, es decir, las circunstancias en las cuales el método daría el mayor de sus resultados sería obteniendo la llamada «*película angiocardiógrafa*», desde el comienzo del dextroangiocardiógrama al fin del levoangiocardiógrama. Aunque se ha hecho un esfuerzo con éxito para lograr esto en Inglaterra primero y en los E. E. U. U. después, cuando no se tiene ese ideal, basta con placas seriadas, por lo menos dos, para el dextro y para el levo, aunque es fácil disponer de «*seriógrafos*» que pueden obtener cinco o seis placas automáticamente movidas por cada inyección. En los casos fáciles bastaría una sola posición, la ántero-posterior. En los casos difíciles serían necesarias además, la lateral o la oblicua.

Cada malformación cardiovascular simple tiene una imagen típica en el dextroangiocardiógrama o en el levoangiocardiógrama o en ambos. Los casos complejos también la tienen, aunque a medida que las lesiones se van combinando va siendo más difícil apreciarlas todas. En estos casos la exploración muchas veces requiere dos sesiones o hasta más.

Las aplicaciones prácticas del método pueden resumirse en las siguientes formas:

- A. Puede aplicarse para saber frente a un caso clínico dudoso si existe o no un defecto cardio-vascular congénito.
- B. Puede aplicarse a un sujeto que con toda seguridad es un

cardiópata pero se desea confirmar el diagnóstico clínico o se desea saber si existe alguna otra malformación asociada.

- C. Permite conocer las dimensiones y la configuración general de las cavidades cardiacas.
- D. Permite diferenciar las sombras para-cardiacas de la sombra cardiaca evitando los errores posibles.
- E. Permite estimar el tiempo de circulación del ventrículo derecho al ventrículo izquierdo.
- F. Suministra informes sobre la disposición general, dimensiones, número, etc., de las grandes venas cardiacas y del grosor de las paredes ventriculares, etc.

3. Aortografía retrógrada. — Consiste en inyectar un cuerpo radio-opaco desde una de las arterias humerales (casi siempre la izquierda), colocando una banda de compresión en la porción distal a fin de obligar al líquido a que en sentido centrípeto se dirija al cayado aórtico y lo radio-opacifique.

Tiene aplicaciones en los casos de patología del cayado aórtico, conducto arterio-venoso, arco aórtico a la derecha, coarctación, estenosis congénita de los grandes vasos que nacen del cayado, etc.

4. Esófagografía. Este método rinde mucha utilidad en el estudio de las cavidades cardiacas especialmente de la aurícula izquierda y en los casos de arco aórtico a la derecha.

5. Otros métodos. Aquí mencionamos la radiokimografía y la tomografía cada uno con sus indicaciones limitadas dentro de su campo de acción.

6. Cateterismo de las cavidades derechas.

Aunque muchos investigadores habían realizado la introducción de un catéter en la aurícula derecha desde que Forssmann lo hizo en 1929, este método ha tomado una aplicación práctica e importante desde los recientes trabajos de Andrés Cournand, de Nueva York.

Forssmann pensó en que el cateterismo auricular tenía aplicaciones terapéuticas.

Ega de Moniz y su escuela, así como Ameuille y sus colaboradores trataron de opacificar la arteria pulmonar y sus ramas

inyectando yoduro de potasio a través de la sonda. Al método le llamaron «angioneumografía» por creer que el estudio de la disposición de los vasos pulmonares podían servir para el diagnóstico de las neumopatías.

Posteriormente se ha utilizado el cateterismo auricular para obtener angiocardiografías. En el Instituto Nacional de Cardiología de Méjico, Dorbecker, I. Chávez y Celis, obtienen sistemáticamente los angiocardigramas en los adultos inyectando el cuerpo radio-opaco a través de la sonda.

Sodi Pallares, de Méjico, emplea la sonda para obtener el electrocardiograma intracavitario.

Andrés Cournand, obtiene dos datos esenciales con el catéter. En primer lugar la presión sanguínea intra-cavitaria por medio del manómetro de Hamilton y en segundo el estudio de los gases de la sangre. La sonda es radio-opaca y puede seguirse fluoroscópicamente su situación. Puede colocarse dentro de la aurícula derecha o dentro del ventrículo o dentro de la arteria pulmonar misma.

El estudio de estos factores: presión sanguínea y gasometría, permite obtener un concepto exacto de lo que ocurre dentro de las cavidades cardíacas y de aquí su gran aplicación al estudio de las cardiopatías congenitas. Baldwin, Moore, y Seibel, bajo la dirección de Cournand, han dado a conocer resultados convincentes. Otros autores, Dexterm, Burwell, Haynes y Seibel han podido introducir el catéter hasta el tronco de la arteria pulmonar y en sus ramas demostrando una gran arterialización de la sangre contenida en ello. Esto es evidencia de conducto arteriovenoso.

Tenemos la impresión de que este método de investigación tiene una gran precisión y que su práctica es absolutamente necesaria en algunos casos que resultan difíciles de diagnosticar por los métodos existentes en la actualidad.

Sintomatología.

Grupo sin cianosis.

En este grupo hay formas con soplos y sin soplos.

Entre las formas anatómicas que no se acompañan de ninguna clase de soplos mencionaremos de un modo especial a algu-

nos de sus tipos, los más importantes desde el punto de vista práctico.

La dextroposición aislada del cayado aórtico y el doble arco aórtico no se habían considerado hasta una fecha relativamente reciente con el interés que realmente tienen.

Poniendo a un lado los trabajos clásicos publicados hasta hace tres años, fuimos nosotros, los que en el Primer Congreso en México en 1944 llamamos la atención sobre la frecuencia de esta anomalía habiendo presentado en aquella ocasión 7 casos nuevos, 5 de los cuales correspondían a la llamada enfermedad de Corvisart. La forma pura, la que no tiene ninguna otra malformación, es más rara que la asociada, pero es más interesante por los síntomas que puede producir.

Farber, Hope y Robinson, de California, en 1945 demostraron que casos de estridor congénito en el lactante se deben al arco aórtico a la derecha. Después aparecieron los trabajos de Sweet, de Boston y los de Susana Gordon, este último reportando 13 casos de arco aórtico doble.

La disfagia y el estridor congénito, en el lactante, que no parece ligado a ninguna de las causas de estos síndromes, debe ser rigurosamente investigado mediante el esofagograma, los métodos radiológicos en general, incluyendo en algunos casos la angiocardiógrafía.

El gran interés de este grupo de anomalías es la posibilidad de resolver los casos quirúrgicamente.

La microcardia, sobre la cual ha insistido tanto en el adulto Master, es congénita, como lo dice dicho autor. En colaboración con Pereiras hemos señalado casos de evidentes corazones pequeños en el niño; no solamente se trata de diagnósticos anatómicos sino que desde el punto de vista clínico, reúnen las manifestaciones descritas por Master en sus sujetos adultos.

Las anomalías de origen de las arterias coronarias, es rara, pues solo se han descrito unos 30 casos hasta la fecha. Su diagnóstico es electrocardiográfico, siendo imposible por la clínica. El clínico solamente puede descubrir los síntomas de insuficiencia cardíaca.

En cuanto a la llamada hipertrofia cardíaca idiopática, aun-

que el mismo Kujel manifiesta haber casos de evidente confirmación histológica, cada vez que hemos tenido en el lactante un cuadro de cardiomegalia idiopática con su característica evolución grave y rápida hacia la muerte, siempre hemos visto en la autopsia la miocardosis sin inflamación de Kujel.

El bloqueo cardíaco congénito tan ligado a los defectos septales especialmente a la persistencia del foramen oval No. 1 se observa con alguna frecuencia en la clínica. R. Pérez de los Reyes y H. de la Torre en 330 casos lo encontraron 10 veces. En 8 casos el bloqueo era aurículo-ventricular, en 1 caso había bloqueo de rama derecha y en otro caso se trataba de un bloqueo aurículo-ventricular completo, (Enfermedad de Morquio). En estos casos el estudio electrocardiográfico constituye el método de exploración más importante que tenemos hoy.

Las formas con soplos reúnen un grupo de anomalías de una gran importancia.

La enfermedad de Roger, la más frecuente de todas las cardiopatías congénitas, el prototipo de la enfermedad benigna, es de fácil diagnóstico en su forma pura y clásica. La ausencia de trastornos funcionales, su soplo y su thrillolo-sistólico, la configuración cardíaca clásicamente globulosa, su electrocardiograma casi siempre con el eje a la izquierda, es bien característico.

Es un hecho evidente que un tanto por ciento variable de lactantes que en los primeros meses de su vida tienen las características de la enfermedad de Roger típica, se curan clínicamente y quizás anatómicamente. Las observaciones de Parkes Weber, French, Stamm, Still, Muir y Brown, Perry, lo demuestran así; y el propio Weber dió la explicación anatómica. Yo he tenido la oportunidad de comprobar curaciones anatómicas y no simple equilibrios de presiones intra-ventriculares.

El antiguo soplo diastólico de Bard, que a través de las observaciones anatómicas de Brandenburg, en 1934, es la insuficiencia aórtica que da la retracción del tejido fibroso que rodea al agujero de la comunicación, es rara en el niño, hasta el extremo que nosotros no hemos visto ninguna todavía.

Hemos visto dos casos de Roger con el síndrome de Parkinson, Wolff y White (PR corto) que han muerto súbitamente.

La comunicación inter-auricular es mucho menos frecuente que la inter-ventricular.

Como ha demostrado Barclay y sus colaboradores en los fetos y recién nacidos animales, el cierre funcional del foramen oval la mayoría de las veces no cesa en el momento mismo del nacimiento. En efecto, se pueden ver recién nacidos con cianosis los primeros días del nacimiento y una silueta cardíaca agrandada, casi siempre sin soplo que en varias semanas o pocos meses van mejorando, desapareciendo la cianosis y disminuyendo el agrandamiento cardíaco hasta la normalidad absoluta.

Han habido algunas discrepancias entre clínicos antiguos europeos y clínicos modernos sobre algunos puntos sintomáticos de la comunicación inter-auricular. Resumiendo éstas podemos decir que aquellos insistían mucho en la frecuencia de la cianosis y en la ausencia de soplos. El gran Potain, por ejemplo, negaba el soplo. El Prof. Laubry también lo niega. Modernamente, en todas las clasificaciones la comunicación inter-auricular se coloca entre los grupos acianóticos o los cianóticos tardíos y dentro de las formas con soplos.

En nuestra experiencia, la comunicación inter-auricular puede dar formas acianóticas con soplo. Este es sistólico y en los fonocardiogramas es imposible de distinguir del soplo de la enfermedad de Roger. Han habido casos de soplo pre-sistólicos (Martineau, Butin, etc.). Ahora bien, la cianosis en nuestras observaciones o es precoz o es tardía. Precoz, ella se observa en el recién nacido, probablemente por la hiper-actividad auricular del feto y por haber en esos casos una tensión intracavitaria derecha mayor que la izquierda, condición que desaparece días o semanas o meses después. Tardía, está descrita desde Bard, Curtillet, Frikett y otros más. Esto explica por que en la clasificación de la Dra. Abbott se incluye en los casos de cianosis tardías.

En cuanto a la silueta cardíaca, en los casos de recién nacidos y lactantes pequeños, predomina la imagen grande de cavidades derechas de gran diámetro. La imagen de gran tamaño de la arteria pulmonar y arco medio saliente y corazón con tendencia al tipo de Sabot, es muy rara en nuestras observaciones.

Las anomalías de las cavas en defectos del septum inter-

auricular son muy frecuentes especialmente cuando hay dextrocardia.

Esta anomalía puede persistir toda la vida en forma muda.

Puede también curar anatómicamente aun teniendo el niño varios meses de enfermedad de lo cual tenemos comprobaciones angio-cardiográficas.

De la enfermedad de Lutembacher tenemos 3 casos en el niño y uno en una adulta joven.

La persistencia del conducto arterio-venoso es acianótica, muchas veces sin trastornos funcionales durante muchos años. La hipotrofia general del paciente, el soplo sisto-diastólico con refuerzo diastólico a nivel de la extremidad anterior del 3er. espacio intercostal izquierdo, la tensión arterial con una diferencial amplia, el agrandamiento cardiaco con salida del arco medio, etc., forman un conjunto típico.

Teniendo en cuenta estos elementos sintomáticos, Hubbard, de Boston, ha dividido con un sentido quirúrgico los casos de esta enfermedad en dos tipos llamados: compensado y descompensado. El descompensado es el que tiene la presión diastólica baja, signos periféricos de regurgitación, hipertrofia cardíaca, congestión pulmonar y gran retraso en el desarrollo físico de los pacientes.

El soplo sistólico puro es muy raramente observado. (Mannheimer describió dos casos estudiados con fonocardiografía calibrada.)

Bohn ha insistido en la importancia diagnóstica de la caída de la mínima durante el ejercicio de los enfermos.

Es la cardiopatía congénita más amenazada por la infección secundaria principalmente estreptococo viridans.

La muerte de los casos sobreviene por infección del conducto o por insuficiencia cardíaca e incompetencia de las sigmoideas pulmonares.

La coarctación de la aorta forma otra entidad típica sin cianosis. El soplo sistólico del segundo espacio intercostal izquierdo, los amplios latidos del cayado aórtico a nivel de la horquilla esternal, la circulación arterial suplementaria en las axilas y espacios intercostales, el aumento de la tensión arterial en las extremidades superiores, etc., forman un conjunto típico.

En el recién nacido y el lactante muchas veces el diagnóstico es imposible, porque la dilatación arterial compensadora y sus signos indirectos no se ha realizado todavía.

La sombra cardiaca permanece normal y hay un ligero aumento de las cavidades izquierdas.

Grupo con cianosis.

Entre las formas que tienen soplos tenemos una serie de ellas interesantes casi todas anatómicamente complejas.

La combinación de estenosis pulmonar, comunicación interauricular y comunicación inter-ventricular, llamada Trilogía de Fallot, forma una entidad definida y sin embargo no se destaca bien por los autores sajones. Hemos encontrado 10 casos confirmados por angiocardigrafía o por la autopsia o por ambas cosas a la vez.

En estos casos la cianosis es ligera, el soplo es mesocárdico, sistólico, y la silueta cardiaca es globulosa con un arco medio siempre pronunciado.

La Tetralogía de Fallot que tanta prominencia ha adquirido últimamente por sus posibilidades quirúrgicas, es un complejo frecuente. En todas las estadísticas es la más frecuente entre las lesiones asociadas.

El enfermo es cianótico siempre, discreta o intensamente. El soplo es mesocárdico, pudiendo transmitirse a los vasos del cuello. Hay distrofia cardiopática y trastornos funcionales en proporción a la insaturación de la sangre en oxígeno, silueta cardiaca normal en tamaño o ligeramente disminuida. La imagen típica en el ortodiagrama es el corazón «en sabot», un arco medio cóncavo, arco aórtico prominente a la derecha del mediastino superior. Es frecuente el signo de Danelius (ausencia de hilio radiológico). La dilatación difusa de la arteria pulmonar (signo de Denzer y Horn) es muy rara, casi excepcional. Sin embargo hay casos que tienen siluetas atípicas con un desarrollo anormal de las cavidades derechas especialmente de la aurícula (Castellanos y O. García). La aorta puede ser hipoplásica y no dilatada como está descrito clásicamente. Puede haber en casos aislados (sin

que sean necesariamente Complejo de Eisenmenger) dilatación de la arteria pulmonar. (White.)

Se llama Enfermedad de Corvisart a aquellos casos que poseen arco aórtico a la derecha además de los cuatro componentes de la tetralogía de Fallot. Clínicamente son indiferenciables. Cuando en una enfermedad de Corvisart la aorta se encuentra hipoplasia, el diagnóstico puede ser muy difícil con la tetralogía pura, a no ser que el esófagograma de una imagen típica. En estos casos la angiocardiógrafía es decisiva.

La estenosis pulmonar pura es una afección relativamente rara. Debemos consignar que, como ha sido señalado por Brumlick, la mayoría de las veces es acianótica. En efecto cuando ella es moderada y la función cardíaca es normal, no provoca cianosis. Los tipos II y III de nuestra clasificación, que tienen gran estenosis la presentan de un modo constante, por lo menos cada vez que el enfermo hace un esfuerzo.

El diagnóstico es fácil en todos los casos pues la semiología física, el ortodiagrama y el electrocardiograma son siempre típicos.

La atresia tricuspídea asociada a la persistencia del foramen oval y muchas veces a la comunicación inter-ventricular también, da origen a un cuadro típico de cianosis, soplo mesocárdico y desviación del eje eléctrico a la izquierda. Encontrar en un cianótico el eje eléctrico a la izquierda sugiere siempre esta combinación porque la hipoplasia ventricular derecha determina prácticamente un corazón trilobular funcional con predominio de desarrollo de las cavidades izquierdas.

La transposición de los grandes vasos (forma completa, no corregida o cruzada) puede existir con o sin comunicación inter-ventricular. Generalmente hay comunicación. El soplo es casi la regla así como la cianosis intensa en este tipo. El corazón tiene un pedículo estrecho casi siempre y su forma es globulosa. Es frecuente grandes cambios en la onda T en todas las derivaciones debido al nacimiento de las coronarias de la aorta implantada en el ventrículo derecho, recibiendo por lo tanto sangre venosa y determinando una anoxia del miocardio al igual que sucede en los casos de anomalías del nacimiento de las coronarias cuando éstas nacen de la arteria pulmonar normalmente implantada.

En los corazones triloculares la cianosis es generalmente discreta o moderada: es más frecuente en el tipo mono-ventricular que en el mono-auricular. Generalmente el soplo no existe. La cianosis se debe a la mezcla de sangre venosa con sangre arterial, pero desde el punto de vista angiocardiográfico nosotros hemos demostrado que es frecuente comprobar, cuando existe un solo ventrículo, la sangre venosa procedente de la aurícula derecha se aplica contra la pared derecha de la cavidad única ventricular mientras que la que desciende, ya oxigenada, de la aurícula izquierda, se aplica contra la pared izquierda del ventrículo único, mezclándose, en la parte media de esta cavidad ambas sangres, venosa y oxigenada, en mínima proporción. La mezcla de ambas sangres se realiza más fácilmente en los casos con auricular únicas que en los casos mono-ventriculares.

La silueta cardíaca es muy variable semejando unas veces a la trilogía y otros a la tetralogía de Fallot.

El tronco arterial primitivo persistente puede ser parcial o total. A veces produce poca cianosis durante meses o años. — Generalmente no tiene soplo pero pueda haber soplo sistólico indiferenciable del soplo del conducto arterio-venoso (Mannheimer).

Pronóstico.

Depende en general del tipo anatómico en particular y de la perturbación fisiopatológica que crea. Es por esto que la insuficiencia cardíaca es menos marcada en ciertas formas acianóticas que en otras. Por ejemplo, en la enfermedad de Roger.

Circunstancias patológicas como la endocarditis o endoarteritis subaguda, las embolias paradójicas y los abscesos cerebrales determinan en muchos casos la muerte de los enfermos.

En pronóstico de cada afección varía para cada una de las formas anatómico-clínicas y esto hace muy extenso su estudio.

Tratamiento. Aspecto médico.

El problema de las endoarteritis y endocarditis infecciosas por estreptococos viridans, bacilos hemófilos, influenzae, brucelas, etc. ha sufrido una evolución distinta en virtud del advenimiento de los sulfamídicos, y antibióticos.

En relacion con los estreptococos, se sabe hoy en día que cuando ellos son sensibles a la concentracion de O. I. de unidade Oxford o menos, generalmente el tratamiento a base de penicilina es efectivo. Asi lo han demostrado los trabajos de Wolferth y sus asociados, (1945), Bloomfield y Halpern (1945), Loewe (1945), Christie, de Londres, en 1946 etc. — El empleo de los anticoagulantes se ha discutido muchos, teniendo muchos adeptos, Friedman, Hamburger y Katz, Loewe y colaboradores etc.

Afortunadamente, los resultados obtenidos por Priest y McGee, con la estreptomycin en 1946, han venido a demostrar que razas bacterianas penicilino-resistentes pueden ser dominadas con la estreptomycin.

Aspecto quirurgico.

Los grandes adelantos de la Cirugia realizados por la Escuela americana principalmente, han venido a poner en el tapete el tratamiento paliativo o definitivo de muchas formas anatomicas de malformaciones cardio-vasculares.

La primera enfermedad congenita dominada por la Cirugia fué el conducto arterio-venoso. La escuela de Boston, con Gross, demostró que la persistencia del conducto era posible tratarla de un modo radical. La historia de este tratamiento puede dividirse en dos fases, la primera con la ligadura simple o doble del conducto; la segunda, con la seccion completa del conducto. Esta ultima es la unica que se aconseja hoy.

En el Vigésimo Sexto Meeting de la Asociacion Norte-Americana para la Cirugia de Torax, Gross presentó — una relacion de 133 casos operados de los cuales la ligadura se hizo en 43 casos. En 90 casos se hizo la division completa del conducto. Crafoord, de Stocolmo presentó 71 casos, la mitad con la seccion completa del conducto. Wagstein operó 33 casos.

La infeccion del conducto es capaz de curar aproximadamente la mitad de los casos solamente con la ligadura (Touroff y asociados).

Las cardiopatias cianóticas en las cuales existe estenosis o atresia pulmonar han sido abordadas desde 1946, por Taussig y Blalock. — Hasta principios de 1947, la escuela de Baltimore

solamente tiene operados 144 casos, con 118 anastomosis. La mortalidad operatoria ha sido de 22 %. En la anastomosis se empleó la arteria ignominada en 36 casos con 12 muertes. La subclavia se utilizó en 72 casos, con solo 6 muertes.

El principio del metodo consiste en anastomosar una gran arteria sistémica a la arteria pulmonar a fin de conducir sangre al territorio vascular pulmonar. — El metodo se emplea exclusivamente en aquellos casos en los cuales la anoxemia y la cianosis, poliglobulia etc. se debe a la estenosis o atresia pulmonar. Se indica tanto en casos puros como en casos asociados, tetralogía de Fallot, etc.

La coarctación de la aorta fué operada por primera vez por Crafoord, de Estocolmo en 1944 habiendo reportado en esa fecha los dos primeros casos operados con éxito.

En 1945 Gross publicó sus primeros dos casos. En el Vigésimo-sexto mitin de la Sociedad Norte-americana para la Cirugía del Tórax, Gross reportó haber operado ocho casos con dos muertes y cinco buenos resultados.

Casos de coarctación de la aorta con persistencia del conducto arterio-venoso han sido operados con éxito por Crafoord.

Por último, Gross, en 1946, estableció, las variedades anatómicas de arco aórtico a la derecha o de doble arco aórtico que deben operarse para librar a los enfermos de las molestas manifestaciones de esta enfermedad.

Es de esperarse que dentro de muy pronto otras formas de defectos cardiacos puedan ser también abordadas por la cirugía.

Conclusiones.

10. Aunque es completamente imposible que las distintas formas anatómicas de defectos cardiacos congénitos puedan ser colocadas en grupos y sub-grupos invariables, es imprescindible aceptar una clasificación. Tomando como base las de Variot, Abbott y Cossio, hemos hecho una clasificación que incluye algunas formas no descritas hasta ahora.

20. Las formas sin cianosis son las más frecuentes. En la estadística de R. Pérez de los Reyes y H. de la Torre, del De-

partamento de Cardiología del Hospital Municipal de Infancia de La Habana predominaban las formas sin cianosis en la proporción de 2 : 1.

De las formas sin cianosis la más frecuente es la enfermedad de Roger y después la Bilogía «tipo I» de nosotros.

De las formas cianóticas la más frecuente es la tetralogía de Fallot.

30. Son frecuentes relativamente otras anomalías del desarrollo. La sífilis congénita clásica existió 9 veces en 330 casos.

40. Las formas debidas a detención del desarrollo en alguna parte de las estructuras cardio-vasculares quedan sin explicación en una gran proporción de casos. La acción del virus de la rubéola demostrada por Grebb y Swan explican un pequeño contingente de estas anomalías. La influencia de deficiencias vitamínicas (Warinsky) y el papel de las reacciones antígeno-anticuerpo materno-fetales considerados por Levine no se ha comprobado aún. La influencia de la sífilis directa o próxima explica un pequeño número de casos. Debe considerarse la influencia de la sífilis lejana aplicando el criterio due Grenet llama «tele-sífilis». La influencia de la herencia nuevamente puesta en el tapete por Green necesita ser estudiada de un modo especial.

50. El electrocardiograma, el fonocardiograma y la gasometría sanguínea, son exploraciones de una importancia extraordinaria. Delimitadas indicaciones son el flebograma, el tiempo de velocidad circulatoria, la manometría venosa, el cardiograma y otros métodos.

Entre los métodos radiológicos la determinación de la silueta cardíaca y de los distintos diámetros tiene un gran valor aunque sus conclusiones no siempre son definitivas para establecer diagnósticos anatómicos exactos. El esófagograma, la quimografía y la tomografía tienen indicaciones restringidas.

De extraordinaria importancia es el método angiocardio-gráfico de Castellanos y Pereiras cuya técnica rápida y sencilla está al alcance de todos los pediatras, cardiólogos y radiólogos. Su uso sin embargo está contra-indicado en los casos que tienen insuficiencia cardíaca importante y síndrome cardio-vascular debido a grandes desviaciones del mediastino. Sin embargo, la

cianosis intensa no la contra-indica. El mejor estudio patogénico de los efectos determinados por la inyección rápida del cuerpo radio-opaco en la circulación y la respiración por un lado, y por otro el descubrimiento de sustancias más tolerables pronto ampliarán las aplicaciones prácticas del método.

60. El cateterismo de las cavidades derechas al poder determinar la presión de la sangre en la aurícula y ventrículo derechos así como la composición gasométrica de la misma se ha impuesto como un método, con el cual hay que contar para la resolución de casos clínicos difíciles de diagnosticar.

70. Entre las formas sin cianosis mencionaremos la dextroposición aislada del cayado aórtico y el doble cayado aórtico a la cual se le ha dado extraordinaria importancia últimamente al demostrar Gross que pueden ser abordadas por la cirugía, la microcardia congénita sobre la cual ha insistido Master en el adulto, las anomalías de origen de las arterias coronarias de la que hay aproximadamente descritos unos 30 casos, la llamada cardiomegalia idiopática, el bloqueo cardíaco congénito tan unido a los defectos septales y pudiendo llegar al bloqueo auriculo-ventricular completo (Enf. de Morquio).

Entre las formas que tienen soplos la más frecuente es la enfermedad de Roger cuyas características generales permanecen invariables. La comunicación inter-auricular clásica es acianótica, tiene un soplo característico y una silueta cardíaca bastante constante, pero pueden tener cianosis tardía o muy precozmente. La persistencia del conducto arterioso se ha agotado en su estudio por ser una cardiopatía quirúrgica y lo mismo la coarctación de la aorta.

Entre las formas que tienen cianosis, la trilogía de Fallot es poco destacada en la literatura sajona mientras que la tetralogía de Fallot se ha estudiado profundamente desde todos los aspectos especialmente por constituir una anomalía que puede ser mejorada profundamente por la cirugía. La estenosis pulmonar en grado moderado no da cianosis pero sí en los grados intensos. La atresia tricúspidee tiene el interés de poder ser por lo menos sospechada por la electrocardiografía. La transposición de los grandes vasos casi siempre existe con comunicación inter-ventricular.

Entre los corazones triloculares son más frecuentes los mono-ventriculares. En estos tipos la cianosis no es muy intensa por mezclarse solamente una moderada cantidad de sangre en la parte media del ventrículo único. El tronco arterial primitivo puede ser parcial o total. En algunos casos hay poca cianosis en los primeros tiempos habiéndose descritos casos con soplos continuos.

80. El pronóstico depende de la perturbación fisiopatológica que crea cada tipo anátomo-clínico de cardiopatía y de la aparición de las complicaciones como la endocarditis o endoarteritis infecciosa, las embolias paradójicas y los abscesos cerebrales. La infección secundaria precozmente diagnosticada tiene un pronóstico extraordinariamente mejor desde el empleo de la Penicilina y de la Estreptomicina, los anticoagulantes, etc.

90. La cirugía ha permitido resolver de un modo definitivo los casos de conducto arterio-venoso persistente, de coarctación de la aorta y los de arco aórtico a la derecha además de doble arco aórtico.

En el grupo de los grupos cianóticos, aquellos que tienen estenosis o atresia pulmonar experimentan una gran mejoría con la operación de Taussig Blalock.

Es por este motivo que el diagnóstico anatómico tiene que establecerse de un modo exacto. Para esto se cuenta hoy en día con métodos precisos los cuales realizan el milagro de poder determinar el tipo de anomalía con una gran seguridad.

Co-RELATOR.

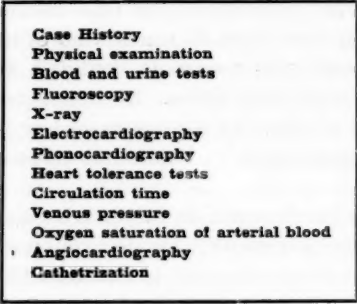
On the Clinical Diagnosis in Congenital Heart Disease.

By **E. Mannheimer, M. D.**

From the pediatric clinic of the Crown Princess Lovisa's Children's Hospital, Stockholm. (Head: A. LICHTENSTEIN.)

The clinical diagnosis in medicine is like a puzzle the pieces of which represent different examination methods. Fig. 1 shows the methods routinely used in congenital heart disease.

Dr. CASTELLANOS has just told us about his outstanding angio-



Case History
Physical examination
Blood and urine tests
Fluoroscopy
X-ray
Electrocardiography
Phonocardiography
Heart tolerance tests
Circulation time
Venous pressure
Oxygen saturation of arterial blood
Angiocardiography
Cathetrization

Fig. 1. Examinations methods.

cardiographic studies and in a while Dr. Cournand will speak about his grand work on cathetrization.

Without underestimating the great value of these tools, I have chosen to say some words about the clinical value of fluoroscopy, phonocardiography and the hypoxia tolerance test.

Fluoroscopy has been systematically studied by many roentgenologists and cardiologists but no one has had the same extensive experience as Dr. Helen Taussig of Baltimore. I am mostly indebted to her for lending me her fluoroscopic diagrams.

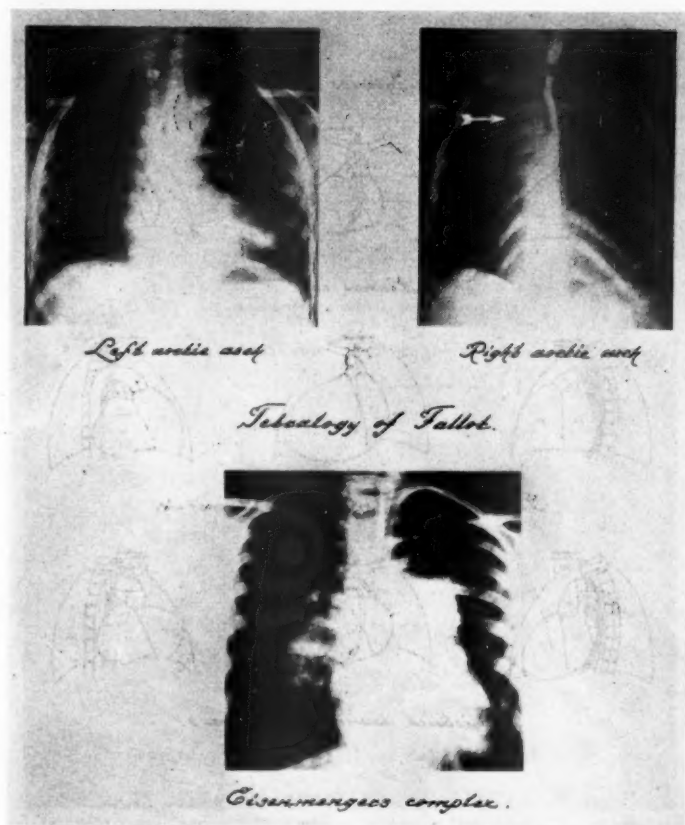
In the cyanotic group (*morbus ceruleus*, blue babies) you may among other distinguish four of the most common types of malformations, namely tetralogy of Fallot, Eisenmenger complex, transposition of the great vessels and persistent truncus communis. Each of these types has its own typical fluoroscopic picture.

In most cases of tetralogy of Fallot (pulmonary stenosis, septal defect, overriding aorta and hypertrophy of the right ventricle) the left border of the heart is mostly concave, the pulmonary conus is decreased in size or lacking, the lung fields are clear without pulsations. In twenty per cent of the cases the aorta is ascending on the right side. The surgeon must have correct information as he has to operate upon the side opposite to the aorta. Right incision in cases with left aortic arch and vice versa.

In cases of Eisenmenger complex (septal defect, overriding

a

b



c

Fig. 2. X-ray in a) tetralogy of Fallot with left aortic arch, b) tetralogy of Fallot with right aortic arch, c) Eisenmenger complex.

aorta, and a dilatation of the pulmonary artery) the fluoroscopic picture is quite another one. The pulmonary conus is often bulging, and you will find the vessels in the lung fields pulsating. It is of great importance carefully to look for pulsations.

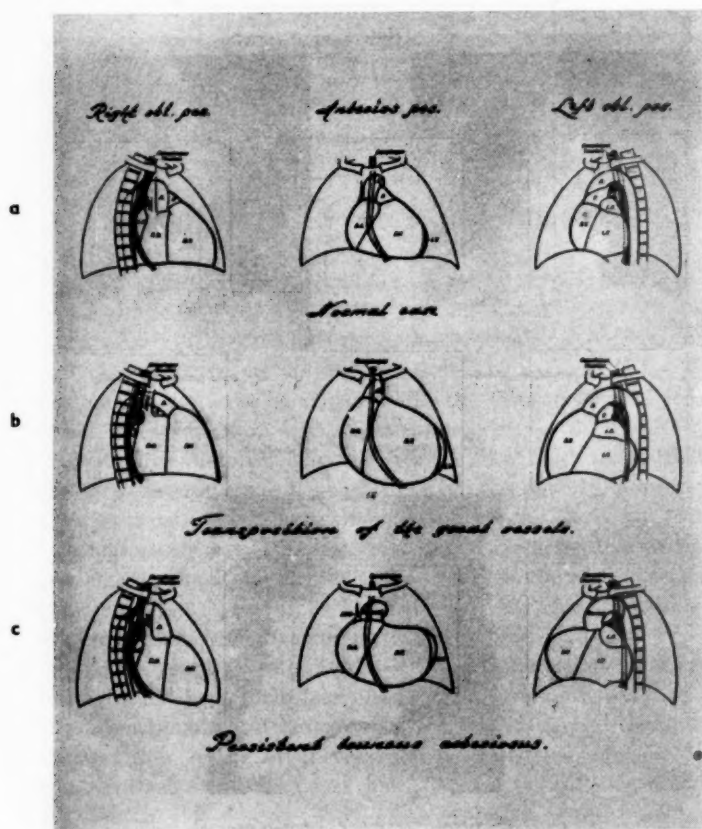


Fig. 3. Fluoroscopic diagrams in a) normal infant, b) transposition of the great vessels, c) persistent truncus communis. (acc. to Helen B. Taussig.)

If you in a blue baby will find pulsations the case should not be sent to operation without further examination (cathetrization, angiocardiography a. s. o.).

Fig. 3 shows the fluoroscopic diagrams of the heart in a normal infant, in one case of transposition of the great vessels and in one case of persistent truncus communis.

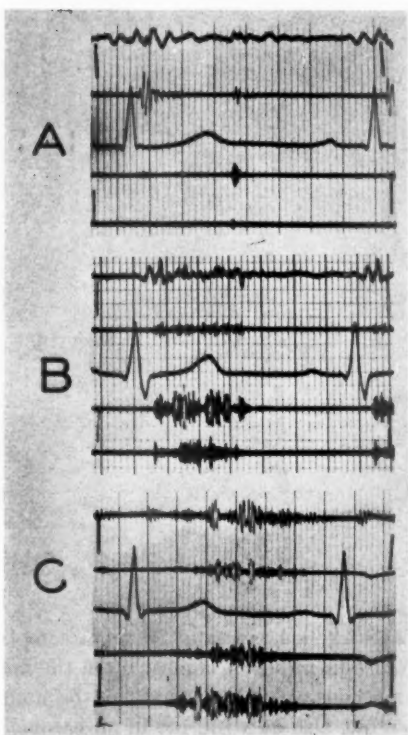


Fig. 4. Phonocardiograms: A) normal case, B) ventricular septal defect, C) patent ductus arteriosus.

In transposition of the great vessels the aorta is ascending directly in front of the pulmonary artery. Both vessels will be overshadowed by the column. Together with an enlarged heart and an extreme cyanosis the diagnosis is given (Taussig 1938).

In persistent truncus communis the fluoroscopic picture shows a wide shadow of the great common artery and the much enlarged right ventricle, the shape of which makes an angle of about 90 degrees.

These few examples may give you an idea of the value of

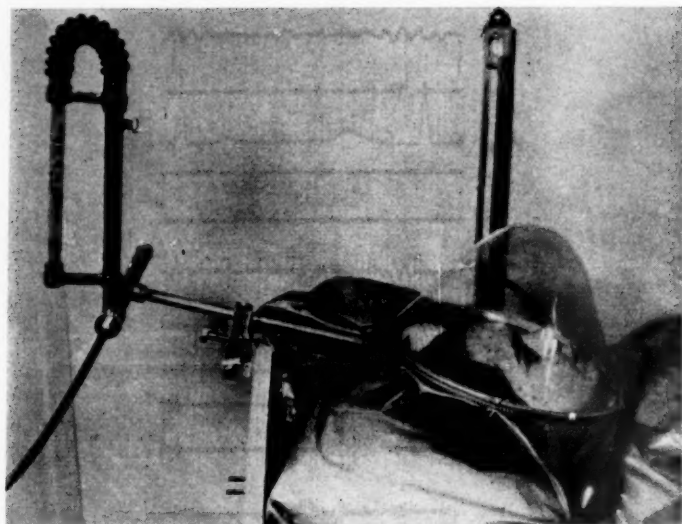


Fig. 5. Hypoxia tolerance test. The apparatus.

fluoroscopy. The method is useful in most cases of congenital heart disease. In blue babies it is most often the most important of all clinical methods available. It should be used not only by roentgenologists but also as a routine in all cardiac clinics. Skillfully performed fluoroscopy might in many cases of congenital heart disease give the correct diagnosis of the malformation.

Phonocardiography has been studied in our clinic for more than ten years. Our aim has been to measure the amplitude and pitch of the sound phenomena of the heart. Calibrated phonocardiography makes it possible in many cases to differentiate between normal and pathological sounds and murmurs. The amplitudes are expressed in absolute units that is dynes/cm². We have until now taken more than 10 000 tracings.

Fig. 4 shows one normal case, one case of ventricular septal defect and one case of patent ductus arteriosus.

The normal case shows the physiologic systolic murmur, which

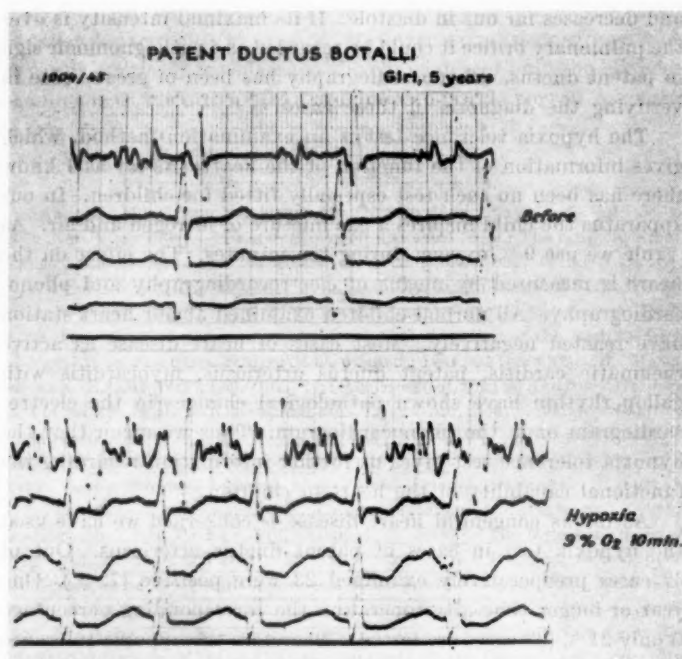


Fig. 6. Patent ductus arteriosus. Electrocardiographic changes during hypoxia 9 % 10 minutes.

could be recorded in all normal children (McKee 1938, Mannheim 1940). It is low pitched and has a small amplitude. The presence of a systolic murmur in normal subjects should lead to a careful judgement of slight systolic murmurs. The systolic murmur in the case of a ventricular septal defect has a much higher frequency and a bigger amplitude.

In the case of patent ductus the continuous murmur is recorded. As a rule its intensity is great especially in lower frequencies. It does not begin directly after the first sound as stated in literature. In all of our 150 cases the continuous murmur begins in the middle of systole, has its crescendo up to the second sound

and decreases far out in diastole. If its maximal intensity is over the pulmonary orifice it could be regarded as a pathognomonic sign in patent ductus. Phonocardiography has been of great value in verifying the diagnosis in these cases.

The hypoxia tolerance test is an examination method, which gives information of the function of the heart. As far as I know there has been no such test especially fitted for children. In our apparatus the child inspires a gas mixture of nitrogen and air. As a rule we use 9 % oxygen during ten minutes. The effect on the heart is measured by means of electrocardiography and phonocardiography. All normal children examined at our heart station have reacted negatively. Most cases of heart disease as active rheumatic carditis, patent ductus arteriosus, myocarditis with gallop rhythm have shown pathological changes in the electrocardiogram or in the phonocardiogram. Thus we mean that the hypoxia tolerance test gives us further information regarding the functional capability of the heart in children.

As far as congenital heart disease is concerned we have used the hypoxia test in cases of patent ductus arteriosus. Out of 32 cases preoperatively examined 23 were positive (72 %). One year or longer time after operation the corresponding percentage is only 21 % (33 cases are tested). Therefore the hypoxia tolerance test in patent ductus gives us possibilities objectively to judge the improvement made by operation.

In Stockholm cases of congenital heart disease have been surgically treated. Dr. CRAFOORD, who in 1944 made the first operation in coarctation of the aorta has until now operated upon 17 such cases with 2 deaths and upon about 100 cases of patent ductus with 3 deaths. Dr. Sandblom at our clinic has made the Blalock-Taussig operation in tetralogy of Fallot in 3 cases with no deaths. Our experiences in Stockholm agree with the american authors. The surviving patients without cyanosis are cured, the blue babies are much improved by this outstanding progress in surgery.

Ladies and Gentlemen, this short revue given in 10 minutes could only give you superficial information about some of the methods available in congenital heart disease. The more special

tests that will be used the more we need cooperation with workers in other departments than ours. However we must not forget that as far as diagnosis is concerned the clinician and only the clinician should deal with the cases and be responsible for all measures taken.

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CO-RELATOR.

Contribution to the Symposium on Congenital Heart Disease.

By Dr. André Cournand, New York.

(Abstract.)

By introducing into the venous system a radio-opaque catheter it is possible (a) to explore under fluoroscopic control the contours of the right chambers of the heart and of the pulmonary

artery; (b) to demonstrate directly any abnormal communication (a) between the right and left side of the heart; (c) to sample blood for oxygen determination and to record blood pressures in the various parts of the heart and large vessels of the base where the tip can be directed. Exact location of the tip of the catheter is ascertained by an immediate analysis of the blood pressure records obtained.

This technique is used in combination with an indwelling needle placed into a peripheral artery for blood sampling and blood pressure recording; and with the collection of expired air for the measurement of oxygen intake it provides data for the calculation of blood flow through (a) the right auricle, (b) the right ventricle, (c) the pulmonary artery, and (d) the systemic circulation and of blood shunts inside the heart and in the accessible proximal portion of the pulmonary artery.

This new method of study of congenital malformation of the heart has been used by various investigators in Baltimore, Boston and New York in well over 200 cases. The use of avertin anesthesia is recommended in young children and infants in order to maintain basal conditions during the prolonged period of study (about 2 hours). In this group also, the catheter may have to be introduced into the venous system through the internal saphenous vein at the femoral region, whenever the veins of the arms are too small.

The clinical benefits to be expected are (1) more accurate diagnoses than by conventional methods, especially in cases where several anomalies are present; (2) more precise indications for operation when cardiac surgery is contemplated; (3) a more comprehensive understanding of the effects of congenital heart disease on the dynamics of the heart and circulation.

Although in the hands of experienced investigators the method has proved its safety, the possibility of complications such as vascular thrombosis or cerebral air emboli in cases of Tetralogy of Fallot should be borne in mind.

Discussion.

Rigoberto Aguilar, M. D., Mexico.

The contribution of Castellanos and co-workers (1—3) to the diagnosis of congenital cardiopathies with their method of angiocardiography, has been valuable and fruitful.

Their interesting results have been the inspiration for further research by American authors, (4—10) who have extended the application of the method to adult cardiopathies, and to the work carried on at the National Institute of Cardiology of Mexico by Drs. Ignacio Chávez, Narno Dorbecker und Alejandro Celis (11) who, following a new technic, have managed to obtain a highly opaque contrast resulting in very beautiful images, both in children and in adults.

The new technic referred to, consists in the dissection of the external jugular vein under local anesthesia, and the introduction through it of a rubber catheter directly into the right auricle, or right ventricle if desired. Then, the radiopaque substance (70 % solution of diodrast) is injected. The circulation time, «right heart-tongue», must be determined, and according to it, a rapid series of overexposed films is taken at intervals which vary with the image one wishes to obtain, be it of the right cavities and/or pulmonary circulation, or of the left cavities and/or general circulation.

The images obtained of the right heart, by this method, are excellent, but the ones obtained of the left cavities, aorta and its branches, are really beautiful, and have never been attained by other of the usual methods.

With the precision allowed by a greater contrast, it has been possible to confirm some known facts and to discover others such as the images of the right and left cavities both in systole and in diastole. The constitution of the middle arc of the cardiac silhouette by the left branch and not by the pulmonary artery proper. In the patent duct arteriosus, the filling of the main trunk of the pulmonary artery or its left branch takes place not by the filling of the right cavities, but by a back-flow from the aorta through the fistulous connection between the two vessels. Besides, for the first time it has been possible to visualize the isthmie stenosis of the aorta, and to obtain a good filling of aneurysms, thus permitting to establish the differential diagnosis from tumors of the mediastinum.

Using the technic described, a presentation is made of some of the images obtained.

Fig. I. Anteroposterior image of the right cavities. Taken at the end of the injection of the radiopaque substance.

The right auricle and ventricle are clearly visualized, as are the

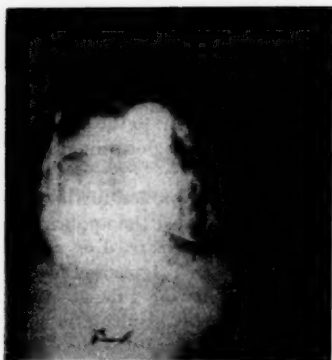


Fig. I.



Fig. II.

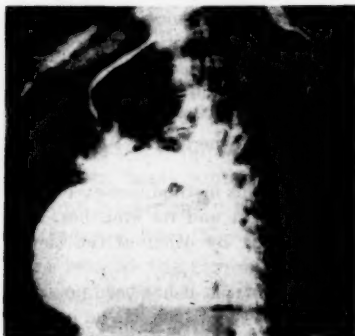


Fig. III.

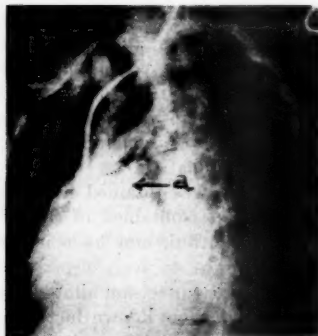


Fig. IV.

infundibulum, the pulmonary artery proper, and its right and left branches with their main ramifications.

Fig. II. Image of the left cavities.

Taken seven seconds after the injection of the radiopaque substance. Shows the pulmonary veins, the left auricle and ventricle, the arch of the aorta and its descending portion, and the brachiocephalic artery.

Fig. III. Case of patent duct arteriosus.

Image taken at the end of the radiopaque injection.

Shows very clearly the right cavities, the main trunk of the pulmonary artery, and its branches.

Fig. IV. Case of patent duct arteriosus.

Image taken six seconds after the injection of the radiopaque substance.

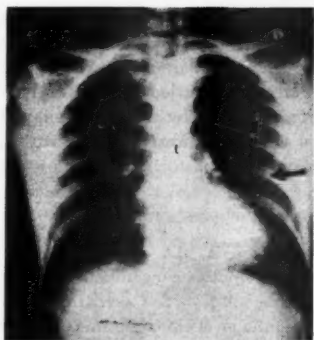


Fig. V.

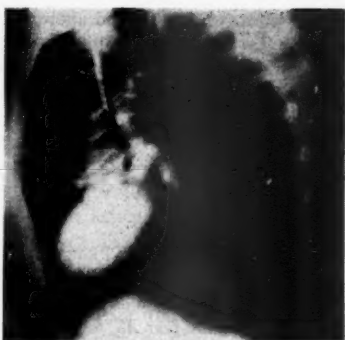


Fig. VI.



Fig. VII.

The left cavities, the aorta and the brachiocephalic trunk are visualized, and in «a», is seen the shadow produced by the filling of the pulmonary artery which normally should not be seen at this moment. This constitutes an indirect sign evident of a patent duct arteriosus.

Fig. V. Case of isthmus stenosis of the aorta.

The ordinary X-ray film taken with a Bucky diaphragm, shows Roesler's sign of costal erosion, and only a slight enlargement of the left ventricle.

Fig. VI. Case of isthmus stenosis of the aorta.

Image taken four seconds after the radiopaque injection.

The ascending aorta is seen widened, the radiopaque image stops

at the limits of the descending aorta, besides, the image of the left cavities and of the pulmonary veins is seen reaching the left auricle.

Fig. VII. Case of isthmic stenosis of the aorta.

Image taken six seconds after the radiopaque injection.

It shows a dilatated ascending aorta followed by a spindle-shaped dilatation continued below by a narrow thoracic and abdominal aorta. The left ventricle appears almost empty.

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Dr. Ivan Hecko, Bratislava, Czechoslovakia.

Under certain circumstances cyanosis can be of great help in the diagnosis of the kind of vitium cordis in a vitium cordis congenitale. For in some cases, cyanosis is not even, but more pronounced on the upper or the lower part of the body. This persistent preponderance of cyanosis in one part of the body appears as a result of certain anatomical, or rather pathological-anatomical changes of the heart. A diagnosis, established in such cases upon a characteristic clinical picture will agree with the

result of the autopsy in every detail. The two enclosed scheme-drawings try to show the heart in the case of a persistent, uneven cyanosis.

The first scheme shows the transposition of the great vessels. The aorta arises from the right ventricle, the pulmonalis from the left. The systematic circulation, supplied with blood from the right ventricle, returns the venous blood to the right auricle and the right ventricle. The pulmonic circulation, coming from the left ventricle, returns the oxygenated blood to the left auricle and the left ventricle. There are here then two separate circulations; the systemic and the pulmonic; in the first, the blood should be practically without oxygen, in the second, one would expect only arterial blood. In a newborn infant, however, the fetal communications are open. Thus it happens that 1. from the right auricle, a certain quantity of blood may get through the foramen into the left auricle and 2. from the arteria pulmonalis through the ductus Botalli into the aorta. And so either, as in the first case, venous blood gets mixed with arterial blood, or, as in the second case, arterial blood gets mixed with venous blood. The heart and the upper part of the body are thus supplied from the arising aorta and from the aortic arch with blood which is practically unable to supply the tissues with oxygen. The lower part of the body gets from the descending aorta mixed blood — blood partly oxygenated by the blood from the arteria pulmonalis. The cyanosis therefore is more conspicuous on the upper part of the body.

Of course the upper part of the body is supplied — as Naegeli and Blumenfeldt have stated — with some oxygenated blood by the anastomoses between the pulmonary veins (with oxygenated blood) and the bronchial arteries which latter are emptied into the vena azygos; this vein leads into the vena cava superior. The heart and the upper part of the body have thus a very low oxygen content, the lower part of the body gets more oxygen. If this kind of vitium cordis happens to be combined with some other kind of vitium — a defect of the ventricular septum for example — this combination makes the uneven cyanosis disappear partially or even completely. The oxygenated blood coming from the left heart is mixed in such cases with venous blood already in the right ventricle.

A cyanosis of the lower part of the body could appear in the case of a stenosis of the isthmus of the aorta, if the stenosis were localized above the mouth of the wide open ductus Botalli (scheme number 2).

In such a case the upper part of the body would be supplied with oxygenated blood from the left ventricle, mixed with some venous blood flowing through the foramen ovale from the right to the left auricle. This lower part of the body would get for the most part venous blood, flowing from the pulmonary artery out by way of the broad ductus Botalli into the aorta, avoiding thus pulmonic circulation.

Lindemann and Gruber have described 2 cases of cyanosis of the first

kind (with a preponderance on the upper part of the body) in 1919. From among the patients, treated at the First Clinical Hospital for Children of Prof. Brdlik in Prague, I have selected 2 cases, observed in the years 1936 and 1937.

The first of the infants died 53 days old. The roentgenograms of the heart were made on the 5th, the 30th and the 45th day after birth. The second infant died when 7 days old, the roentgenograms were made on the 5th day after birth, the first in the inspirium, the second in the expirium. In both cases, the clinical diagnosis was confirmed by the autopsy: The first patient showed a transposition of the great vessels. Sepsis. Otitis media purulenta bilat. A septic tumor of the spleen. Cyanosis of the upper part of the body. Hypostasis of the lungs.

The second patient showed a vitium cordis congenitum. Transposition arter. vera. Morbus coeruleus. Colitis follicularia. An intimation of arachnodactylia. Hypostasis lobi inf. lat. utr. pulm.

A case, in which theoretically a cyanosis of the lower part of the body was to be expected, was observed also. Unfortunately, the infant got aspiratory bronchopneumony immediately after birth. Due to this, probably, there was no difference between the cyanosis of the upper and the lower part of the body. The baby died 5 days old.

The autopsy showed: The course of the common branch of the arterial septum was asymmetrical, the pulmonary artery was dilated and the aorta was narrow with a stenosis of the isthmus. The ductus Botalli was very broad. The right heart showed hypertrophy. Two half-moonshaped valves were in the aorta and in the pulmonary artery (all cases dissected at the Institute of Prof. Kimla).

The following part is meant to serve as information for the participants of the Congress, but will not be discussed. It brings the description of two cases of uneven cyanosis, with a preponderance of cyanosis on the upper part of the body.

1. Patient R. V. (entered at the hospital under number 9033/1936, number of the doctor's report 711) was brought 5 days old from the lying-in hospital to the clinical hospital for children. The baby had a light cyanosis from the first day of its life. When it was brought to the clinical hospital for children, the cyanosis did not show on the lower part of the trunk, the thighs and the shanks. Later on it changed in intensity, increasing on the whole, getting ante finem very intensive. Between the upper part of the body, which was more cyanotic, and the lower part, which was less cyanotic, there would appear from time to time, especially if the baby was quiet, a rather sharp horizontal line, about 1 and 1/2 cm above the navel. This line was more conspicuous in the front than in the back. The heart showed a dilatation (clinical as well as on the roentgenogram) to the left, only very little to the right. Later on, it became enlarged on both sides, relatively more, however, on the right side, as far as

nearly acquiring the characteristic shape of a ball, but with a rather broad shadow of the great vessels. Ten days after birth, a systolic murmur was heard above the pulmonalis, clearly audible in the left axilar region. Four days later it disappeared and was heard again faintly on the 27th day after birth (one day only), along the left border of the sternum. One day ante finem — 52 days after birth — once more a faint murmur was to be heard in the left axilar region. The heart sounds were not changed much, but for a more pronounced second sound near the left border of the sternum between the second and the third intercostal space. From the 19th day on, there was an easily perceptible pulsation in the xifoid region.

The capillarscopic test showed: Broad subpapillary veins, cyanosis and a continuous, comparatively smooth flow in the slings of the capillaries.

The haemogram showed: On the 8th day after birth a bleeding-time of 10 minutes, on the 30th day of 5 and 1/2 minutes, ante finem of only 2 and 1/2 minutes. The coagulation time and the retraction of the coagulum were always normal. The number of trombocytes on the 8th day was 331 000, on the 30th day 450 000, ante finem 210 000. The number of erythrocytes and the content of haemoglobin decreased from 5 270 000 and 111 % to 4 768 000 and 105 %, ante finem to 4 560 000 and 95 %. The number of leukocytes was 12 450, 6 350 and 10 250. The number of retikuloocytes increased from 4.0 ‰ to 18.1 ‰, then decreased to 13.1 ‰. Nucleated red cell (of the normoblast type) were absent in the blood only ante finem. The haemogram showed ante finem a marked shifting to the left, to myeloblasts (1 %). The resistance of blood-capillaries, after a haemostasis of ten minutes and after a lowering of the atmosphere pressure (by means of a suction ball) did not show any changes.

The urine showed: Pyuria (with bacillum coli) in the beginning with an exceedingly great number of leukocytes in the sediment and a mild albuminuria; ante finem hyaline cylinders appeared, while the pyuria was strongly receding.

2. Infant H. A. (entered at the hospital under number 9961/1937, number of the doctor's report 123) was born cyanotic and because of increasing cyanosis was taken from the lying-in hospital to the clinical hospital for children when only two days old. In the beginning the cyanosis was comparatively even, but on the 4th and 5th day of life, it began to show a preponderance on the upper part of the body. On the day of exitus (7th day after birth) this cyanosis on the upper part was clearly predominant. No cardiac murmur was audible. The heart sounds were limited, the first on the apex was resounding, the second above the pulmonalis accentuated. On the left lower border of the sternum, a pulsation was to be felt by touch. The haemogram showed a marked shifting to the left, many erythroblasts of the normoblast type (20 erythroblasts: 100 leukocytes). L 22 150 E 4 784 000. The bleeding-time, coagulation-

time, the number of trombocytes, the retraction of the coagulum and the resistance of capillaries were normal. The roentgenogram showed a dilatation of the heart to the left with a marked pulmonary arch in the inspirium.

Dr. John D. Keith, Toronto, Canada.

In discussing these papers I would like to point out how frequently these various types of heart disease occur in children. This slide shows the prevalence of common defects noted in our Cardiac Clinic at Toronto. Congenital heart disease was just as common as Rheumatic Heart disease. Functional or accidental murmurs also constituted a major group.

It has been a great pleasure to come to the Meeting and hear some of the details of the work of Dr. Cournand, Dr. Mannheimer and Dr. Castellanos.

Re. Dr. Cournand:

Dr. Cournand has provided us with a wealth of information of a fundamental nature with his use of the intracardiac catheter. A year ago I visited him for the first time. His courteous reception of visitors and his willingness to discuss the problems fully in spite of his busy routine has put many of us in his debt. This Congress is primarily interested in the application of Dr. Cournand's methods to congenital heart disease. By the catheter one can carry out the best diagnostic investigation for interauricular septum and interventricular septum. One can also work out with accuracy the amount of blood flowing through a patent ductus arteriosus. The catheter does not help in coarctation of the aorta. It is useful, however, in problem cases with cyanosis, as has been shown by Dr. Cournand and his assistants and by Dr. Bing in Baltimore, when volume of flow through pulmonary artery, aorta and collateral vessels can be determined with reasonable accuracy. Dr. Cournand had developed an oxygen consumption test in exercise that has proved valuable in congenital heart disease. When there is reduced pulmonary flow there is usually a decrease in oxygen consumption per liter of air ventilated. The reverse is true for normal individuals.

Re. Dr. Mannheimer:

A glance at the slide indicates how commonly functional or accidental murmurs are found. Dr. Mannheimer's work provides us with a new understanding of certain aspects of these murmurs. The demonstration that the accidental murmurs are usually in the 50—175 frequency level fits in with our clinical impression that they have a characteristic low pitched scratchy sound. I am particularly interested to note that he finds this murmur in 70 % of normal children by Phonocardiogram and that 40 % are audible with the stethoscope. He points out that the pre-

sence of this first heart sound makes it difficult to hear some of the short murmurs. This reminds me of many cases when the first heart sound is poorly heard, in such instances a short faint systolic murmur can often be heard. Dr. Mannheimer's approach to the study of heart sounds and murmurs is a fascinating one.

Re. Dr. CASTELLANOS:

Dr. Castellanos opened up a field 10 years ago that is promising to be a most useful adjunct to our diagnostic procedure in congenital heart disease. The rapid injection of Diodrast into the circulation allows one to decide 2 important points in cyanotic children. (1) Whether there is a shunt from the right ventricle in the Aorta, (2) Whether the pulmonary artery fills from the right ventricle. A wealth of additional information can be obtained but these essential features are notably available in most cases. This procedure is easier and safer than catheterization during the first year of life. Its subjective detail in studying a case is most welcome. On the other hand the catheter studies have the advantage that the collateral circulation can be determined, a part of the circulation that cannot be determined by angiocardiography.

However, rather than comparing these methods I would like to point out the importance of considering all available information in each case whether it is from the clinical findings or laboratory.

This case of an 11 day old infant with cyanosis and a systolic murmur illustrates this point. The shape of the heart in X-ray suggests its diagnosis. The Electrocardiogram confirms it and the Angiocardiogram demonstrates clearly that we are dealing with a non functioning right ventricle. Dr. Castellanos' method is a great source of pleasure to me when investigating cases of congenital heart disease. It reveals so many interesting defects. I am glad to acknowledge this debt.

Maurice Lamy (et Melle **O. Schweisguth**), Paris: *Enquête familiale dans 156 cas de cardiopathies congénitales.*

Les difficultés qui sont communes à toutes les études de génétique médicale sont particulièrement graves dans le domaine de malformations humaines. Les malformations du coeur sont souvent d'un diagnostic difficile et d'une classification malaisée. Ces difficultés reconnues, nous avons quand même fait une enquête interrogatoire familiale de 156 cas de cardiopathies congénitales.

Nous avons recherché tout d'abord l'existence d'autres malformations chez les individus atteints d'une cardiopathie congénitale. En second lieu, la présence des malformations cardiaque et non-cardiaques dans l'environnement familial des malades.

En ce qui touche l'existence de malformations associées chez les malades nous avons constatée des malformations très diverses. La constatation

que nous avons faite avec le plus de fréquence est celle d'une arriération mongolienne. En effet, 6 de nos 156 malades étaient des mongoliens. Il ne s'agit pas en réalité d'un fait nouveau, et l'on connaît depuis longtemps la fréquence des malformations congénitales du coeur chez les mongoliens.

Dans 15 familles, nous avons retrouvé au moins un autre cas de malformation cardiaque. Le plus souvent, 8 fois, et quelle qu'ait été la malformation présentée par le malade c'est une cyanose congénitale que nous avons retrouvée dans son entourage familial.

A 4 reprises, nous avons vu 2 générations atteintes en ligne directe. Chez une mère et sa fille, nous avons observé la persistance de canal artériel. Nous avons observé une mère porteuse d'un situs inversus total et dont la fille avait succombé à des accidents de cyanose congénitale. Nous avons examiné une femme atteinte d'un rétrécissement aortique congénital dont le fils était porteur d'un situs inversus. Enfin, nous avons examiné un enfant atteint d'une maladie de Roger (communication inter-ventriculaire) dont le grand-père était porteur lui aussi d'une malformation indiscutable du coeur.

Dans tous les autres cas il s'est agi d'une malformation constatée en ligne collatérale. Certes, l'hérédité directe, notée dans certains cas, plaide en faveur d'une transmission monomérique dominante simple. D'autre part, l'existence, dans une fratrie, de deux sujets atteints d'une malformation cardiaque et issus de parents sains, évoque la possibilité d'une hérédité du type récessif. L'élévation du taux des mariages consanguins dans l'ascendance appuierait, on le sait, cette opinion. En fait, nous avons trouvé 7 fois sur 156 cette notion de consanguinité; un pourcentage très élevé que pourrait être considéré comme significatif. Deux fois seulement il s'agissait d'une consanguinité dans l'ascendance directe. Une statistique fondée sur des chiffres aussi faibles est passible de critiques.

Enfin notre enquête a recherché dans l'entourage familiale du malade, l'existence d'autres malformations que celles du coeur. Nous avons relevé un nombre important de tares diverses: pieds-bots, fragilité osseuse, luxation de la hanche, syndactylie, surdi-mutité, diabète et mongolisme. On peut dire que, dans certains cas au moins, la malformation du coeur est d'ordre constitutionnel et héréditaire et qu'elle s'explique par la possession d'un ou de plusieurs gènes pathologiques.

Il nous paraît douteux que toutes les malformations congénitales du coeur puissent être considérées comme d'essence génotypique. En effet, la confrontation des jumeaux monozygotes donne des résultats qui contredisent cette opinion.

Nous dirigeons depuis plusieurs années, à l'Hôpital des Enfants Malades de Paris, une consultation spécialisée qui nous a permis déjà d'observer plus de 600 couples de jumeaux. A 3 reprises nous avons constaté une discordance chez des jumeaux dizygotes, mais, fait beaucoup

plus important, nous avons noté à 2 reprises, une discordance chez des jumeaux monozygotes.

Dans le premier cas il existait chez l'un des enfants une communication interventriculaire, alors que son frère jumeau était certainement indemne, dans le second cas, nous avons noté chez une fille une malformation volumineuse de l'artère pulmonaire alors que sa soeur jumelle n'offrait aucune anomalie à l'examen.

De telles discordances s'inscrivent contre la these génotypique et suggerent fortement l'intervention d'un facteur extérieur, périnatal, ayant exercé son action pendant la vie intra-utérine.

Nous avons cherché d'abord si l'âge de la mère pouvait être considéré comme l'un de ces facteurs, comme dans le mongolisme. Nos recherches n'ont pas abouti à des résultats décisifs.

En ce qui concerne l'action possible d'une maladie infectieuse contractée par la mère pendant les premières semaines de sa grossesse nous n'avons pu obtenir de renseignements utilisables que dans 85 cas sur 156, mais, fait intéressant, il nous a été signalé à deux reprises le développement, au premier mois de la grossesse, d'une fièvre éruptive possédant plusieurs des caractères de la rubéole. Dans ces deux cas les enfants étaient atteints d'une malformation congénitale, difficile à classer, mais qui s'accompagnait chez le premier d'une microphthalmie avec cataracte et chez le second d'une surdité. Or, ce sont la précisément les malformations associées qui ont été signalées par Gregg, par SWAN, par CARRUTHERS, par REESE et par d'autres auteurs encore.

L'enquête que nous avons poursuivie autorise croyons-nous quelques conclusions provisoires. Certaines malformations paraissent bien être constitutionnelles et héréditaires, d'essence génotypique. D'autres, au contraire, sont sans doute la conséquence d'une action extérieure à l'individu exercée pendant la vie intra-utérine, et certaines de ces actions sont très probablement de nature infectieuse.

Enquêtes généalogiques consciencieuses, l'utilisation de statistiques étendues, la confrontation des jumeaux monozygotes, une étude plus fouillée des facteurs susceptibles d'agir pendant la vie intra-utérine, l'emploi de toutes ces méthodes éclairera une question qui aujourd'hui demeure entourée de beaucoup d'obscurités.

Thursday, 17th July.

19 o'clock. The banquet of the Congress was held in the Waldorf Astoria Hotel with the President, Professor HENRY F. HELMHOLZ, presiding. At the banquet following speeches were held:—

Lee F. Hill, M. D., President, American Academy of Pediatrics:—

As president of one of the sponsoring organizations of the Fifth International Pediatric Congress, I am sure the Academy would want me to express its pleasure and its thanks that so many of you have found it possible to come to America to make this one of the most, if not the most, outstanding pediatric meetings of all time.

In November, 1944, at one of its national meetings the Academy unanimously adopted the following objective — »to make available to all mothers and children in the United States of America all essential preventive, diagnostic, and curative medical services of high quality which, used in co-operation with other services for children, will make this country an ideal place for children to grow into responsible citizens«. At the same time, it authorized a nation-wide study or survey for the purpose of collecting factual information concerning existing medical facilities and services for children. The study, now in progress, is being carried on with the co-operation and assistance of the United States Children's Bureau and the United States Public Health Service. A special phase of the study is being directed toward improving pediatric education.

At the conclusion of the study, a great deal should be known about the medical facilities and services available, or lacking, for the children of America. Upon the basis of this information it should be possible to plan constructively to correct and improve

conditions for all children wherever need has been demonstrated. The Academy clearly recognizes the importance of a follow-up or action program to implement the information obtained and already has appointed a committee through which it is hoped that the best possible care can be given to all children.

We, as members of the Academy, believe that in this project we are accepting our responsibility to all of the children in the United States.

Professor **Arvid Wallgren** (Stockholm):—

Mr. President, Ladies and Gentlemen:—

It is a great honor for me to have the privilege to speak to you at this occasion. I have been asked to tell you in a few words how we care for the well-being and development of all of our Swedish children.

The ultimate aim of our child's welfare program is that every child, irrespective of the parents' social position, financial circumstances, or place of residence, should be afforded the possibility of development under conditions which are medically, socially and humanly satisfactory. This we try to accomplish by grants given to the mother from the State and Community, by systematic education of the mothers in the care and nursing of their infants, by routine control of the development and health of the children, by adequate hospital and institutional care of sick and physically and mentally handicapped children.

The country-wide prenatal care and delivery facilities in maternity hospitals aim at giving every child a good start in life in regard to its health. In communities where there is a qualified pediatrician, he is in charge of all newborn infants in the maternity hospitals. This is regarded as a most important accomplishment.

After their return home, the mothers are given guidance in the feeding and care of the children by trained visiting health nurses belonging to the child health centers which are spread all over the country. The health centers are headed by a qualified pediatrician if such is available or by well trained health officers, who control the development and well-being of the children from

birth on. The attendance is without cost and voluntary, with the exception of foster children and infants whose mothers receive grants from the State. In average, about 80 per cent of all infants are supervised by these health centers. When the child attains school age, the responsibility of his well-being is transferred to the school health service, which exists in every school and works in about the same way as the health center for children of pre-school age.

The hospital care in Sweden has always been organized in that way that almost all the costs are paid by the community in order to make the best of medical care available to all. In a few years all hospital care in Sweden will be quite free. At the same time, the now voluntary health system is to be transferred into a compulsory one providing medical care without any cost and permitting the mothers a free choice of physician. In every province in Sweden there is a Central Hospital and most of them have special wards for children's diseases, with a qualified pediatrician as head physician. This pediatrician is supposed to be responsible for the health center and the children's institution in the province.

Our program for the mental care of the children is still incomplete. At present it is provided by child guidance clinics which as yet, because we lack sufficient numbers of psychiatrically trained pediatricians, are available only in some communities, but are to be established at the Central Hospital of every province. For mentally and physically handicapped children we have a number of special institutions providing satisfactory care and education. Through the above mentioned preventive measures and therapeutic facilities as well as the high standard of living, we are making conditions as ideal as possible in which our children can develop to their maximum capacity.

We pediatricians from the whole world assembled at this Congress constitute a unit of nations. We may have different opinions in minor scientific problems but our opinion is unanimous as to the principal object of our profession: the welfare and the satisfactory development of all children of the world.

Victor Escardó Anáya, M. D. (Uruguay):—

Dr. Helmholtz, ladies and gentlemen:

It is a privilege for me to represent at this closing banquet all of the Latin American attending this magnificent world Congress.

I wish that I could express to those present something of what the Latin spirit has given and should give to the world — that spirit which is a ray of divine light in the beacon of culture and of civilization.

This Congress and the earlier one in Washington have shown clearly what the pediatricians have done for the children of our American countries. Institutions that coordinate the activities of all the Americans such as the American Institute for Protection of Childhood, of which I am Secretary, must continue their efforts so that all children may find happiness.

There remains however much that we must do if all children of the world are to have their rightful opportunities. The future will be good if the children of to-day are healthy in both the material and in the spiritual sense.

May it please God that the world of the future may rest upon a foundation of today's children nurtured in health and in peace.

We hope that all this may be extended to the children of all the world.

— — — Soñamos con que todo lo que ha realizado la pediatría moderna puede ser extendido a todos los niños del mundo.

— — — Nous désirons que tout ce qui a été fait par la pédiatrie moderne puisse être étendu a tous les enfants du monde.

— — — Noi desideriamo che tutto quanto è stato pediatria moderna possa essere esteso a tutti i bambini del mondo.

— — — Wir hoffen dass die Fortschritte der Kinderheilkunde dem Wohle aller Kinder der ganzer Welt zu gute kommen.

— — — Sovremionnaja pediatrija dolzhna obespetschito rezkoje snischenie smertnoctio detec rannievo vosrasta j polnoje iszhitiye ostrich infektsio.

Dr. Robert Debré (Paris):—

Monsieur le Président, Mesdames, Messieurs.

Vous avez voulu, Monsieur le Président, que l'adresse des représentants des différentes Nations, que vous avez invitées au Cinquième Congrès International de Pédiatrie, soit prononcé en langue française. Je vous remercie pour cette pensée de courtoisie, dont je suis heureux, non pas seulement parce que la langue choisie est celle de mon pays, mais à cause de tout ce que la langue française représente dans le Monde. Son passé est un des plus riches qui furent jamais, elle a apporté au trésor intellectuel de l'humanité des pages de prose et de vers, de pensées et de rêves parmi les plus puissantes, les plus pures et les plus belles. C'est dans les oeuvres de nos écrivains, que vos ancêtres de toute l'Amérique ont puisé les idées, qui sont à la base même de vos constitutions et de votre vie publique. Vous n'oubliez pas que vos savants doivent lire en français les textes de Lavoisier, fondateur de la chimie moderne, de Claude Bernard, fondateur de la physiologie moderne, de Louis Pasteur, créateur de la bactériologie, de Monsieur et Madame Curie, fondateurs de notre physique contemporaine et que vos aînés furent instruits en français par Laennec, Louis, Bretonneau . . .

Mais les idées françaises ne sont pas confinées dans le passé le plus noble. Elles sont à l'heure présente aussi vivantes que jamais et l'avenir du monde, pour une grande part, dépend de l'écho qu'elles auront dans l'esprit des peuples. Ces idées, trois grands mots les résument: liberté, égalité et fraternité. Egalité entre tous les hommes et toutes les femmes de toutes les races, de toutes les religions, de tous les pays; fraternité entre tous les hommes et toutes les nations et liberté, liberté pour laquelle les Nations se sont unies devant le péril de l'esclavage le plus horrible et se sont battues. Liberté, dont les trois syllabes évoquent notre chant national et ce cri d'amour que la France a jeté et qui bouleversé le monde: «Liberté, Liberté chérie! . . .»

C'est donc en français, Monsieur le Président, que j'exprimerai, au nom de tous mes collègues, deux idées très simples, celle-ci tout d'abord: il nous paraît impossible que la première réunion

internationale de tous les pédiatres du monde, d'hommes et de femmes penchés sur les souffrances des enfants, préoccupés du bien-être des enfants, soucieux de la vie heureuse des enfants, n'ait pas une pensée de souvenir et de respect pour la mémoire des enfants qui, dans nos pays occupés par des ennemis implacables, ont souffert de la faim, du froid, de la misère, de la maladie, des enfants qui ont été maltraités, blessés, massacrés, des enfants qui ont subi le martyre affreux des camps de concentration, des enfants — c'étaient presque des enfants ces jeunes hommes qui sont tombés dans le combat de la Libération, des enfants — c'étaient presque encore des enfants ces héros clandestins qui ont subi les pires tortures dans les prisons parce qu'ils s'étaient levés pour défendre leur propre pays et la liberté de tous.

La seconde pensée que je voudrais exprimer aussi au nom de tous mes collègues — que je remercie de l'honneur qu'ils me font en me choisissant pour parler en leur nom — est celle-ci: nous n'avons pas seulement admiré pendant ce Congrès, la magnifique envolée de la science américaine, l'esprit scientifique des chercheurs, et des médecins de ce pays, la richesse des installations hospitalières vouées à l'enfance par la générosité américaine, la beauté de votre exposition biologique et clinique, qui a demandé un si grand effort. Ce qui a soulevé en nous le sentiment le plus vif: c'est la cordialité de votre accueil, c'est la gentillesse de votre hospitalité, c'est la délicate attention, manifestée à nous tous. Vous avez fait une belle oeuvre en fortifiant des sympathies anciennes, en créant de nouvelles sympathies, ou plutôt, j'ose employer ce mot, sur lequel je terminerai, en scellant et en fondant des amitiés.

Dr. Edwards Park:—

The Fifth International Congress is about to end. For us, your hosts, it has been a notable occasion. Many of us have had the pleasure of renewing acquaintance with old friends — speaking for myself, I name only that indomitable spirit and wonderful example, Dr. Gorter of Leyden — and of being able to see and to listen to and perhaps to form the beginnings of friendship with thinkers and workers in our field, some of them world famous men

whose names are hospital ward and laboratory words. It has been a source of great regret to me personally that owing to language difficulties I was unable to talk to our Russian colleagues. I should like to have been instrumental in making them feel the most cordial welcome to this country and to this Congress and to have taken the first steps toward the establishment of, I need hardly say that, lasting personal friendship. Many of my American friends feel exactly as I do. Then there has been the opportunity to talk informally among ourselves. A medical congress like this is not so important for the transmission of knowledge as for the opening of doors to new ideas and to new sources of knowledge and for the establishment of new lines of communication for the passage of new conceptions and methods.

When the American Committee met to decide when to have the Congress, I was opposed to holding it this year. I thought that the world had not recovered sufficiently from the war to collect itself and put together the broken fragments of the past. But I was mistaken. The sooner and the more completely the past can be turned into the present, the quicker the return to normal sane ways of life. There is no way to forget like to work. A congress like this which gives at once a wide perspective of the needs of the children throughout the world and makes new knowledge, conceptions and methods to meet those needs the common possession of all of us, is the quickest way to start erecting the new edifice out of the ruins of the old. In accomplishing this, we pediatricians occupy the strategic position amongst physicians for our task lies at the foundation of human life. It is not our duty to hold up the tottering older generation but to safeguard and develop the new. We pediatricians have always been foremost in the practice of medicine since we have always been the leaders in the employment of preventive medicine. The science of medicine has developed so fast that it has outstripped its social and economic applications. In consequence ideas concerning medical care are undergoing a revolution and in this the prevention of disease is assuming a dominating importance. We must continue to be the farseeing liberal members of the medical profession, the ones who boldly lead the way in new directions into new fields of usefulness.

But I conceive that our individual duty is more than to attempt to maintain healthy minds in healthy bodies in the oncoming generation but includes also its education in healthy principles and attitudes. It is incumbent on us to use whatever influence we possess to cause the children of the world to grow up believing in the necessity and sacredness of peace, as the Nazi children were taught to believe in the glory and necessity of war, and accepting the principles as axiomatic that differences of opinion between national groups can and must be decided by peaceful means and that ideologies should not be imposed but be left to spread naturally in proportion to their inherent truth. In the last analysis war is caused by greed for power, for the possession and exploitation by pressure groups of the resources of the earth, for the development of prosperity of one national group at the expense of others. So far as I am personally concerned, I would rather lose a war and suffer the consequences than to be the one to release the weapons which we now possess in order to win it. Many of you, our colleagues from Europe and from the Orient, have suffered cruelly and some of you have tasted the horrors of concentration camps. We who have experienced the war will never create war. The danger of war lies in the new generation and the future hope for peace is the attitude of the new generation. We pediatricians cannot teach the philosophy of peace in our professional capacity but only as individuals, but as exponents of it we occupy a unique position of great influence since our work is with children and it is our duty and privilege, as for all high minded people, to teach it with all the energy and conviction which we possess.

Now I wish to thank you all in behalf of my American colleagues for having come to this Congress, in particular those who have honored us most by coming from the most distant parts of the earth, South Africa, India, Siam, Australia, China, and the Philippines. You, our guests, are now about to spread out to the medical centers of this country before returning to your homes. The best way for us to learn to know you and for you to learn to know us is to visit us individually at work in our wards and laboratories. The aftermath of this Congress can be of as much mutual importance and benefit as the Congress itself.

Many of you are to return from this land of plenty and happiness to lands of continued misery and deprivation. But you have made friends with us. Write and let us know how we can help you and we shall respond within our powers. I wish you all success in your work to improve the health and lives of children and for your happiness in so doing, and shall look forward to the next reunion in Zurich three years from now.

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